Novel Multimodality Imaging in the Planning and Surgical Treatment of Epilepsy

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Thesis submitted for the degree of Doctor of Philosophy

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Declaration

I, Mark Nowell, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:
Abstract

Over 50 million people worldwide are affected by epilepsy and in one third of these the condition is poorly controlled by medication. In these patients epilepsy surgery offers potentially curative treatment.

The presurgical evaluation and surgical management of epilepsy is complex. Patients typically undergo a range of imaging modalities, and may also require intracranial EEG (icEEG) evaluation. Cortical resections are informed by these investigations, with the aim of removing the epileptogenic zone (EZ) without causing any functional deficits.

I have investigated the use of 3D multimodality image integration (3DMMI) and it’s relevance in epilepsy surgery in adults. I have supported the use of 3DMMI in our busy epilepsy surgery unit, and demonstrated that disclosure of models changes and informs clinical decision making during presurgical evaluation and surgical planning.

EpiNav™ is custom-designed software for use in epilepsy surgery, representing an image-guided solution to address the complexities of the pipeline. I have incorporated this software into our clinical workflow and demonstrated the potential benefits of computer-assistance in planning depth electrode implantations.

3DMMI and EpiNav have been crucial in the development of the stereoEEG (SEEG) service in our unit. I describe the implementation of frameless SEEG, which forms part of our simplified, image guided pipeline for epilepsy surgery.

Finally, I have gained experience in the generation of optic radiation tractography using constrained spherical deconvolution techniques, which are increasingly used in clinical practice. In a pilot study I demonstrate an association between language lateralisation determined by functional MRI and asymmetry in the position of the anterior bundle of the optic radiation in patients with epilepsy.
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Advanced Investigations in Epilepsy Surgery

Presurgical evaluation of epilepsy

Neuropsychological outcomes

3 Presurgical evaluation of epilepsy

1 Aims of evaluation

2 Patient selection

3 General pathway for presurgical evaluation

Clinical evaluation

Scalp EEG and video telemetry

1 Background

2 Epileptiform discharges

3 Ictal EEG

4 Interictal EEG

5 Quantitative EEG

6 Seizure semiology

6 Structural imaging

7 Neuropsychology

8 Neuropsychiatry

9 Multi-disciplinary team meeting

Advanced Investigations in Epilepsy Surgery

Localising the epileptogenic zone

1 Magnetic Resonance Imaging

2 Diffusion weighted imaging

3 Ictal-interictal subtraction single photon emission CT (SPECT)

4 Positron emission tomography (PET)

5 EEG-fMRI

6 Magnetoencephalography (MEG)

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<tbody>
<tr>
<td>AMT</td>
<td>11C-alpha-methyl-L-tryptophan</td>
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<tr>
<td>3DMMI</td>
<td>3D multimodality imaging</td>
</tr>
<tr>
<td>ATLR</td>
<td>anterior temporal lobe resection</td>
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<tr>
<td>AED</td>
<td>anti-epileptic drug</td>
</tr>
<tr>
<td>AF</td>
<td>arcuate fasciculus</td>
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<tr>
<td>AFA</td>
<td>arcuate fasciculus asymmetry</td>
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<tr>
<td>BOLD</td>
<td>blood oxygen level dependent</td>
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<tr>
<td>CMIC</td>
<td>Centre of Medical Imaging and Computing</td>
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<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<td>CAP</td>
<td>computer assisted planning</td>
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<td>CSD</td>
<td>constrained spherical deconvolution</td>
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<td>CT angiogram</td>
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<td>DCEE</td>
<td>Department of Clinical and Experimental Epilepsy</td>
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<tr>
<td>DTI</td>
<td>diffusion weighted imaging</td>
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<tr>
<td>DNNT</td>
<td>dysembryoplastic neuroepithelial tumours</td>
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<td>EPI</td>
<td>echo planar imaging</td>
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<tr>
<td>ESI</td>
<td>electrical source imaging</td>
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<tr>
<td>EA</td>
<td>electrode accuracy</td>
</tr>
<tr>
<td>ED</td>
<td>electrode deviation</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalography</td>
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<td>EEG-fMRI</td>
<td>electroencephalography-functional MRI</td>
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<td>ES</td>
<td>epilepsy society</td>
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<tr>
<td>EI</td>
<td>epileptogenic index</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
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<tr>
<td>EZ</td>
<td>epileptogenic zone</td>
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<tr>
<td>FSPGR</td>
<td>FastSpoiledGradientRecalledEcho</td>
</tr>
<tr>
<td>FOD</td>
<td>fibre orientation distribution</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid attenuated inversion recovery</td>
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<td>fluorodeoxyglucose positron emission tomography</td>
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<tr>
<td>FCD</td>
<td>focal cortical dysplasia</td>
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<tr>
<td>FA</td>
<td>fractional anisotropy</td>
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<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
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<tr>
<td>G/W</td>
<td>grey/white matter</td>
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<tr>
<td>HARDI</td>
<td>high angular resolution diffusion weighted imaging</td>
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<tr>
<td>HS</td>
<td>hippocampal sclerosis</td>
</tr>
<tr>
<td>HH</td>
<td>hypothalamic hamartoma</td>
</tr>
<tr>
<td>ION</td>
<td>Institute of Neurology</td>
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<tr>
<td>IED</td>
<td>interictal epileptic discharge</td>
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<tr>
<td>ILAE</td>
<td>International League Against Epilepsy</td>
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<tr>
<td>IQR</td>
<td>interquartile range</td>
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<tr>
<td>iMRI</td>
<td>interventional MRI</td>
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<tr>
<td>ICC</td>
<td>intraclass correlation coefficient</td>
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<tr>
<td>ic-EEG</td>
<td>intracranial EEG monitoring</td>
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<tr>
<td>LI</td>
<td>lateralisation index</td>
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<tr>
<td>MRV</td>
<td>magnetic resonanance venogram</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>MEG</td>
<td>magnetoencephalography</td>
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<td>MLTE</td>
<td>mesial temporal lobe epilepsy</td>
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<td>MLA</td>
<td>meyer's loop asymmetry</td>
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<td>MRgFUS</td>
<td>MR guided focused ultrasound</td>
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<td>MRgLITT</td>
<td>MR guided laser interstitial therapy</td>
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<tr>
<td>Abbreviation</td>
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<td>--------------</td>
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<tr>
<td>MST</td>
<td>multiple subpial transection</td>
</tr>
<tr>
<td>NHNN</td>
<td>National hospital for neurology and neurosurgery</td>
</tr>
<tr>
<td>PACS</td>
<td>picture archiving and communications system</td>
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<tr>
<td>QOL</td>
<td>quality of life</td>
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<tr>
<td>RF</td>
<td>radiofrequency</td>
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<tr>
<td>RAM</td>
<td>random access memory</td>
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<tr>
<td>SPECT</td>
<td>single positron emission computed tomography</td>
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<td>stereoEEG</td>
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<td>stereotactic radiosurgery</td>
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<td>subtraction ictal SPECT coregistered to MRI</td>
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<td>temporal horn asymmetry</td>
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<td>temporal lobe epilepsy</td>
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<tr>
<td>TA</td>
<td>trajectory accuracy</td>
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<tr>
<td>USB</td>
<td>universal serial bus</td>
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<tr>
<td>UCL</td>
<td>University College London</td>
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<td>World Federation of Neurosurgeons</td>
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<td>Zuse Institute Berlin</td>
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The incorporation of the EpiNav™ into clinical practice has been supported by the neurophysiologists Beate Diehl and Tim Wehner, and by the neurosurgeons Andrew McEvoy and Anna Miserocchi. I would like to thank the entire clinical team involved in this work with a special mention to Anna who has supported the use of EpiNav™ throughout.

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Gilford, Xandra Harman, Louis Van Graan and Sjoerd Vos. I would also like to thank Gavin Winston for his kind input on optic radiation tractography, and Athena Lemesiou for her invaluable advice on thesis preparation.

Finally, I would like to thank my wife Hannah and our daughter Stella for providing love, encouragement and support throughout my time in research, and I dedicate this thesis to them.
Funding sources

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Outline and statement of personal contribution

In Chapters 1-7 I present an introduction and literature review.

Chapter 1 gives an overview of the history of epilepsy surgery, and explores the different techniques in temporal lobe, extra-temporal lobe and palliative epilepsy surgery.

Chapter 2 describes the outcomes in epilepsy surgery. This is important when considering the risks and benefits associated with surgery in individual patients, and in making the decision on whether to proceed.

Chapter 3 summarises the pathway for the presurgical evaluation of patients for epilepsy surgery.

Chapter 4 describes the advanced imaging modalities that can be used to supplement the basic presurgical evaluation, helping with the identification of the epileptogenic zone and the determination of functional grey and white matter. This also gives an introduction to intracranial EEG monitoring.

Chapter 5 is a more detailed discussion on the technique of stereoEEG, which is increasingly being used to determine the 3D propagation networks in focal epilepsy.

Chapter 6 describes the history and current solutions to using 3DMMI in epilepsy surgery, including a detailed discussion on the AMIRA software that has been used in our centre.

Chapter 7 summarises the future directions that may be taken in the field of epilepsy surgery, with emphasis on the refinement of current methodology, and future neuroablative techniques.

In chapter 8 I summarise the main aims of the thesis and give an overview of the following chapters.
In chapter 9 I describe the generic methods used during these studies. Recruitment and scanning was started by Gavin Winston prior to my arrival and continued by myself from August 2012. Preprocessing of functional MRI data was done by Jane Burdett. I conducted all the preprocessing of diffusion MRI and subsequent tractography. The clinical pipeline for AMIRA image integration and export to neuronavigation systems was established by Christian Vollmar and Roman Rodionov, and I continued this work in the present study. The development of EpiNav™ was led by Prof Sebastian Ourselin’s team that includes Gergely Zombori and Rachel Sparks. The vessel extraction plug-in tool was developed by Maria Zuluaga. I completed all image integration with AMIRA and EpiNav™, with support from Roman Rodionov.

Chapters 10-14 describe the experimental studies that I conducted during this project.

In chapter 10 I describe the outcome from a multi-centre questionnaire on the use of 3DMMI.

In chapter 11 I investigate the usefulness of 3DMMI in clinical practice. I am indebted to the neurophysiology and neurosurgical teams for their participation in this study.

In chapter 12 I examine the potential benefits of computer-assisted planning. Gergely Zombori and Rachel Sparks are responsible for the technical development of the trajectory planner.

In chapter 13 I describe our technique of frameless stereoEEG, and complete a prospective quantitative and qualitative assessment of the accuracy of depth electrode placement.

In chapter 14 I describe an association between language lateralisation determined by functional MRI and Meyer’s loop asymmetry in patients with epilepsy. Scanning and recruitment for this study was done by Meneka Sidhu. Sjoerd Vos performed
tractography of the arcuate fasciculi. I was responsible for calculating language lateralisation indices and generating optic radiation tractography and data analysis.

Chapter 15 summarises the main findings and conclusions, the limitations and future work in this field.
Publications associated with this thesis

Peer reviewed as first author


Nowell M. In response: Talairach methodology in the era of 3D multimodal imaging: “the song remains the same”, but catchier, and therefore more helpful for clinical decision-making and surgical planning in epilepsy surgery." Epilepsia 56(6); 977-998 (2015).


Peer reviewed as co-author


**Submitted**


**Conference abstracts as first author**


**Conference abstracts as co-author**


**Talks**

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Nowell M. Principles of Epilepsy Surgery. International League Against Epilepsy UK Chapter Primary Care Society Meeting 2014.

Nowell M. Principles of anterior temporal lobe resection. Chalfont Journal Club 2013

**Multimedia**


**Book chapter**

1 Principles of epilepsy surgery

1.1 Historical perspective

1.1.1 Early history

The earliest recorded surgical treatment for epilepsy was trephination in patients with post-traumatic epilepsy in Western Europe and North America in the nineteenth century. Dudley reported five patients, who underwent trephination for decompression and debridement at the site of original injury, to ‘remove the cause of cerebral excitation and restore corporeal and intellectual function’ (Dudley, 1832). Three patients became seizure-free and two patients improved post-operatively. Dudley attributed his success to careful patient selection, good surgical technique and the ‘clean, rural Kentucky air’.

1.1.2 Functional localisation

The first significant advance in epilepsy surgery came in the late nineteenth century, with the discovery of cortical mapping and the efficacy of cortical resection for Jacksonian seizures. Sir Victor Horsley, working closely with Hughlings Jackson, considered focal epilepsy as a manifestation of cortical irritability. Informed by their own mapping studies in monkeys, Horsley reported three cases of cortical resection in focal Jacksonian epilepsy (Horsley, 1886). Localisation of the site of surgery was obvious in two patients with skull defects from head injuries. The focal onset in the third patient was correctly identified by Jackson based on seizure semiology, and found to be a tuberculoma in the hand area of the motor cortex. Horsley later demonstrated in vivo cortical mapping, using a bipolar electrode to obtain topographical representation of the motor cortex, prior to cortical resection in a boy with Jacksonian epilepsy affecting the left arm (Fig 1-1). This close collaboration between Jackson and Horsley served as an early template for the close partnership between neurosurgery and neurology, which remains integral to epilepsy surgery to this day.
Further advances with functional localisation were made by Fedor Krause, who made detailed maps of the motor cortex from an extensive series of 96 patients with Jacksonian epilepsy (Krause, 1912) (Fig 1-2). Krause would make wide surgical exposures, and employ faradic stimulation to locate the ‘primary spasming point’, with three physicians present to inspect the face, upper and lower limb of the patient. Krause also noted the importance of ‘delicacy’ around the right arm area to protect speech, and the occasional improvement in neurological deficit that sometimes follows cortical resection.

At the same time Otfrid Foerster, a German neurologist who retrained as a neurosurgeon, developed techniques to better localise seizure onset in patients under local anaesthetic. Foerster would use electrical stimulation, traction on the epileptogenic scar and intra-operative hyperventilation as techniques to elicit the usual seizure pattern (Feindel et al., 2009).

Wilder Penfield was perhaps the most influential neurosurgeon in the advancement of epilepsy surgery. His early work in Oxford with Sherrington, on cortical mapping in primates, led him into the field of neurosurgery. Penfield later wrote, ‘It was the inspiration of Sherrington. He was, so it seemed to me from the first, a surgical physiologist, and I hoped then to become a physiological surgeon’ (Penfield, 1977). Penfield spent six months in his early career with Foerster in Breslau, studying the histology of lesions in post-traumatic

Figure 1-1 Horsley’s sketches of stimulation points on the motor cortex LEFT- at operation, RIGHT- from the excised specimen of cortex (Horsley, 1886)
epilepsy, and proposing a vascular hypothesis for seizure aetiology (Foerster and Penfield, 1930). Whilst there he also learnt Foerster’s surgical techniques of cortical mapping under local anaesthetic. Back in America, Penfield’s work advanced beyond Foerster, creating the celebrated ‘homunculus’ (cartoon of the relative size and order of cortical representation) (Penfield and Boldrey, 1937), and mapping other areas of cortex that subserve speech, hearing, vision and memory (Feindel, 1977).

Figure 1-2 Early drawings of epilepsy surgery
A- Motor map from electrical stimulation. Krause 1912, B- Penfield’s drawings of his first temporal lobectomy (Wilder Penfield Archive)
1.1.3 Early advances in temporal lobe surgery

Penfield describes his first temporal lobectomy as taking place in 1928, using the Foerster technique in a young man with intractable post traumatic epilepsy (Feindel, 1977). The patient underwent three operations in total. At the third operation Penfield resected thin scarred cortex in the temporal lobe, with a resultant improvement in seizure control (Figure 1-2). However, the true advent of temporal lobe surgery would come ten years later, when electroencephalography (EEG) moved into mainstream clinical practice.

In 1936 Frederic Gibbs and William Lennox classified psychomotor seizures as distinct entities to petit mal and grand mal seizures based on EEG findings (Gibbs et al., 1936). They postulated that the presence of a structural lesion was more often the exception than the rule, thus promoting EEG into a strategic position for the diagnosis of epilepsy. Penfield recognised this as a paradigm shift in epilepsy surgery, and established a close and career long working partnership with the neurophysiologist Herbert Jasper at the Montreal Neurological Institute. Jasper suspected that the mesial temporal structures played a role in the origin of seizures, although at this time there was little EEG evidence for this and the function of these structures remained unknown. Jasper performed pre-operative and intra-operative EEG on Penfield’s surgical patients, with a view to localising a visible lesion. If a visible lesion was not found at the place indicated by the EEG, Penfield would usually decline to perform a resection, leading to a 20% rate of excision following exploratory craniotomies in the 1930s.

Between 1939 and 1949 Penfield operated on 68 patients for temporal lobe seizures (Penfield and Flanigin, 1950). All subjects had at least one year follow up. Penfield reported a success rate of just over 50% at curing temporal lobe epilepsy with resections limited to the anterolateral cortex. In some cases persistent seizures prompted Penfield to re-operate, extending his resection to the mesial structures, following the EEG spike activity. It was noted that these structures, including the hippocampus and uncus, were tough, rubbery, slightly yellow and often had a harder texture than expected. A lack of neurophysiological
and histological evidence, as well as uncertainly regarding functional organisation, made surgeons cautious with anteromesial resection (figure 1-3) (Jasper et al., 1951).

Figure 1-3 Localisation of electrocorticographic abnormalities and sites of lesions in patients with temporal lobe seizures operated by Penfield from 1939-1949. The darkest areas indicate maximal abnormalities, which are localised to lateral and anterior temporal regions (Penfield and Flanigin, 1950)

During the 1950s much work was done to investigate the function of the mesial structures, and their contribution to temporal lobe epilepsy. In animal studies, electrical stimulation of the amygdala, head of the hippocampus and pyriform region was found to produce arrests of movement, licking, chewing and swallowing (Kaada, 1951), and epileptogenic lesions were created by injecting aluminium into the mesial temporal structures (Gastaut et al., 1952). In patients undergoing temporal resections, depth stimulation around the amygdala were found to trigger auras and typical seizure features, with ictal amnesia confined to short term memory (Feindel et al., 1952). EEG recordings demonstrated a rapid propagation of
discharges from the claustrum and amygdaloid complex to the anterolateral temporal lobe and other cortex.

Bolder surgery, with resections extended to include the anteromesial structures, played a role in the elucidation of their functional organisation. Milner and Penfield reported a syndrome of defect in recent memory but preservation of intellectual function, in two patients who had undergone unilateral temporal excision in what later became recognised as bilateral mesial temporal pathology (Penfield and Milner, 1958). Based on neurophysiological studies, some bilateral mesial temporal resections were even performed, with a resultant deficit in retaining new memories (Scoville and Milner, 1957). Based on this it became widely accepted that the mesial temporal structures play a key role in memory mechanisms. It is now known that unilateral resection of the amygdala results in no memory deficit, if the contralateral structures are normal, but larger resections of the hippocampus are associated with some detectable memory impairment (Leonard, 1991).

Advances in neurophysiology allied to a greater understanding of functional organisation, led to the widespread adoption of anteromesial temporal resections for temporal lobe epilepsy. In 1952 Penfield published his landmark paper on subtotal temporal lobectomy describing his technique, and concluding that ‘the abnormal, sclerotic area of cortex, which must be removed in most cases, lies in the deepest, most inferior and mesial portion of the temporal lobe’ (Penfield and Baldwin, 1952). Several modifications on this technique have been subsequently described. The advent of magnetic resonance imaging has provided invaluable corroborating evidence, with over 50% of patients with temporal lobe epilepsy demonstrating some structural abnormality.

The anteromesial temporal lobe resection is now accepted as one of the most effective operations in neurosurgery (Wiebe et al., 2001). The more current surgical challenge is in the management of non-lesional focal epilepsies that originate outside the temporal lobe.
1.2 Temporal lobe surgery

1.2.1 Surgical anatomy of the temporal lobe

The neocortex of the temporal lobe consists of five temporal gyri running longitudinally along a grossly circular pattern. These are the superior temporal (T1), middle temporal (T2), inferior temporal (T3), fusiform (T4) and parahippocampal gyri (T5). See Figure 1-4. The hippocampal sulcus runs medial to the parahippocampal gyrus, and pushes against the temporal horn of the lateral ventricle. The most anterior aspect of the parahippocampal gyrus is called the uncus.

Figure 1-4 Anatomy of the temporal lobe.
A-Coronal view shows the circular gyral organisation (T1-T5). Ag: amygdala, I: insula, SF: sylvian fissure(Olivier et al., 2012)

The floor of the temporal horn is formed by the mesial allocortical structures of the temporal lobe. This consists of the hippocampal formation and the amygdala. The hippocampal formation consists of three parts; the subiculum, the hippocampus proper or Ammons horn,
and the dentate gyrus. In transverse section these form an S shape, with the subiculum adjacent to the parahippocampal gyrus. See figure 1-5. The fibre tract of the fornix connects the hippocampal formation to the mammillary body, and forms an important pathway in the limbic system.

Figure 1-5 Anatomy of mesial temporal structures
A-Transverse view of the mesial temporal structures. AG: amygdala, U: uncus, HP: hippocampus, T5: parahippocampal gyrus, OF: orbital frontal cortex, Black arrow indicates middle cerebral artery. Green arrow indicates temporal horn of lateral ventricle. (Olivier et al., 2012)
B- Dorsal view of the hippocampus and parahippocampus. PC: posterior cerebral artery, AC: anterior choroidal artery, HP: hippocampus, CP: choroid plexus. (Olivier et al., 2012)

The intraventricular view of the mesial structures is most pertinent to temporal lobe surgery. The choroidal point is the most anterior part of the choroid plexus that emerges from the choroidal fissure, and marks the point at which the anterior choroidal artery pierces the arachnoid to supply the choroid plexus. The choroid plexus overlies the fimbria, a flat white
band that runs horizontally along the internal border of the hippocampus proper, and separates it from the dentate gyrus. The dentate gyrus is a C shaped grey ribbon that runs parallel and underneath the fimbria and the parahippocampal gyrus. Mobilising the choroid plexus superiorly exposes the fimbria and hippocampus, and is a key step in anteromesial resections. The lateral ventricular sulcus is a shallow sulcus that corresponds to a crease formed by the bulge of the hippocampus proper and the lateral wall of the temporal horn. The hippocampal sulcus separates the various components of the hippocampal formation, and is a further key landmark.

Figure 1-6 Illustration of choroidal fissure
B- To show how the choroid plexus (cp) can be mobilised within the choroid fissure (cf). The black dot within the fissure represents the anterior choroidal artery as it pierces the choroid fissure to enter the ventricle. The choroid plexus (cp) arises from the edges of the choroid fissure. It can be mobilised; lifting upwards exposes the fimbria and hippocampus; lifting downwards exposes the stria terminalis. (Olivier et al., 2012)
1.2.2 Standard anterior temporal lobe resection

Temporal lobectomy indicates the complete removal of the entire temporal lobe including the mesial structures, which is rarely done today. An anterior temporal lobe resection (ATLR) or cortico-amygdalohippocampectomy is a more accurate term to describe the extent of resection.

The standard ATLR was first described by Penfield in 1952, and is also known as ‘The Montreal Procedure’ (Penfield and Baldwin, 1952) (Penfield et al, 1952.) The patient is positioned supine, with the head in three point fixation, rotated approximately 45 degrees, with slight neck extension and dropping the vertex by 20 degrees. A standard pterional craniotomy is performed, with a myocutaneous scalp flap and free bone flap. The dura is opened circumferentially over the proximal segment of the middle meningeal artery, and reflected away from the temporal lobe.

The anterolateral neocortical resection extends from the pole along the superior temporal gyrus to the level of the central sulcus in the non-dominant hemisphere or to the precentral sulcus on the dominant side, which corresponds to 5 or 4.5cm respectively. An en-bloc resection of the anterolateral cortex is performed, extending across the temporal stem to the collateral sulcus separating the fusiform gyrus from the parahippocampal gyrus. The temporal horn of the lateral ventricle is approached via either the middle temporal gyrus or collateral sulcus, increasingly with the aid of neuronavigation. Inside the temporal horn, the key surgical landmarks of the limbic system are made clear by elevation of the choroid plexus to expose the fimbria and hippocampus. An incision is made into the lateral ventricular sulcus, and the parahippocampal gyrus is emptied using the ultrasonic dissector. The hippocampal sulcus is exposed at the medial border of the parahippocampus, and the hippocampus proper is tilted laterally into the parahippocampal cavity. The fimbria is transected subpially along its course, which corresponds to the medial border of the resection. The hippocampus is then rolled and freed from its arachnoid bed, with transection at the junction of the body and tail, and diathermy of the arcade of arteries supplying the
hippocampus. Extending the resection of the parahippocampal gyrus anteriorly beyond the hippocampal sulcus, the uncus is entered. A complete resection of the uncus typically removes 4/5 of the amygdala.

**Figure 1-7 Stages of anterior temporal lobe resection**

A- Coronal view of temporal lobe. Dotted line represents the en bloc lateral temporal surface resection. (Olivier et al., 2012).

B- Lateral and mesial temporal structures removed includes the anterior temporal cortex, amygdala (AG), head and body of hippocampus (HP), uncus and parahippocampal gyrus/subiculum (PHP, sub). In the dominant hemisphere, resection along T1 extends to the precentral gyrus, which corresponds to about 4.5 cm from the temporal tip. In the non-dominant hemisphere the posterior resection margin along T1 is to the central sulcus that is approximately 5 cm from the temporal tip. (Olivier et al., 2012)

C- Coronal view of resection of mesial temporal structures. Resection is subpial, preferably using the ultrasonic aspirator at low settings of suction and amplitude. The first step is entering the lateral ventricular sulcus to empty the parahippocampus. (Olivier et al., 2012)

1.2.3 Selective amygdalohippocampectomy

The selective amygdalohippocampectomy is a modification of the standard Montreal procedure, with a more selective removal of the mesial temporal structures, sparing much of the lateral neocortex. The procedure was first proposed by Niemeyer in 1958 (Niemeyer and Bello, 1973). There have been several technical modifications, including Olivier with the trans-cortical or trans-middle temporal gyrus approach (Olivier, 2000), and Yasargil with the trans-Sylvian approach (Yasargil et al., 1985). This operation is indicated when pathology is limited to the mesial structures. The difference lies in the approach to the temporal horn of
the lateral ventricle. The intraventricular component of the operation, with resection of hippocampus, parahippocampal gyrus, uncus and amygdala, remains the same.

The theoretical advantage of a selective approach is that there is sparing of the lateral neocortex, which may preserve neurocognitive function. This has not been clearly demonstrated with studies that compare selective approaches to the standard ATLR (Adada, 2008, Beaton et al., 2012, Olivier, 2000, Spencer and Burchiel, 2012). One explanation is that selective transcortical approaches still involve substantial cortical disruption. The one truly selective approach is the trans-sylvian route, although this carries risk of procedure-related vascular insults (Martens et al., 2014).

![Diagram of various routes to the mesial temporal structures](image)

**Figure 1-8 Various routes to the mesial temporal structures**
1: trans-Sylvian, 2: trans-T1, 3: trans-T2, 4: subtemporal. (Olivier et al., 2012)

1.3 Extra-temporal Surgery

1.3.1 Lesionectomy

Lesions that can produce epilepsy include areas of cortical dysplasia, tumours (low grade, dysembryoplastic neuroepithelial tumours (DNET)) (Nowell et al., 2015a), areas of cerebral
infarction or traumatic injury, and vascular malformations (Frater et al., 2000). Complete removal of the structural lesion and some of the adjacent cortex yields excellent results. Surgical technique depends on the nature and location of the lesion, but the principles of subpial resection limited to grey matter remain. Peri-lesional resection can be guided by use of intra-operative EEG.

Surgery for focal cortical dysplasia differs from other lesionectomies due to an indistinct border of the structural abnormality. A total resection is made difficult by horizontal encroachment into eloquent cortex, and vertical encroachment into white matter. For this reason intracranial EEG is often performed prior to resection, to guide resection margins and protect eloquent cortex (Roper, 2009).

1.3.2 Hemispherotomy

Hemispherotomy is indicated in patients with unilateral and widespread epilepsy. Common conditions include congenital hemiplegia from a prenatal vascular insult, Sturge-Weber syndrome, hemimegencephaly or diffuse hemispheric cortical dysplasia, Rasmussen encephalitis, hemiconvulsion-hemiplegia-epilepsy, or a sequel of trauma or infection (De Ribaupierre and Delalande, 2008).

The functional hemispherotomy has evolved from the anatomical hemispherectomy, an operation first described by Dandy (Dandy, 1928), but now largely abandoned due to the late complication of superficial cerebral haemosidersosis (Oppenheimer and Griffith, 1966). The goal is the disconnection of corpus callosum, internal capsule and corona radiata, mesial temporal structures and frontal horizontal fibres. This may be achieved by the vertical parasagittal approach (Delalande et al., 2007) or by the lateral or peri-insular approach (Villemure and Mascott, 1995), depending on surgeons’ preference. See figure 1-9.
1.4 Palliative Surgery

1.4.1 Disconnection techniques

The principle of disconnection techniques is to interrupt the epileptic discharge from spreading to the rest of the brain. These techniques are used when the seizures are intractable and resistant to medical therapy, the focus of the epilepsy is widespread and not amenable to surgery, and the natural history of the condition is deemed worse than the post-operative neurological deficit.

1.4.1.1 Multiple subpial resection

In cases where the focus of seizure activity is mapped on sensorimotor or language areas, cortical resection carries a high risk of permanent neurological deficit. Multiple subpial transaction (MST) is a technique that transects horizontal nerve fibres while preserving the intrinsic columnar organisation of the brain (Smith, 1998). This interrupts the synchronisation of epileptic neurons but spares input, output and vascular supply. The technique was conceived by Morrell and colleagues to allow operation on eloquent cortex (Morrell et al.,
The surgical technique requires a specially designed instrument with a 4mm bent tip at 105 degrees. A small opening is made with a 20 gauge needle at the sulci border of the gyrus, and the transector is introduced and swept forward in a vertical orientation. With the tip raised and visible beneath the pial border, the transector is swept back perpendicular to the long axis of the gyrus. Care is taken to avoid injuring cortical vessels and penetrating pia. The process is repeated at 5mm intervals across the entire epileptogenic focus. The poor outcomes with regard to seizure control mean this is rarely done in current practice, and is regarded as a palliative procedure to improve seizure control.

1.4.1.2 Corpus callosotomy

Corpus callosotomy is indicated in patients with intractable generalised epilepsy where one of the main seizures types are atonic seizures or drop attacks. The goal is the section of the corpus callosum. A standard craniotomy and interhemispheric approach is followed by sectioning of the corpus callosum. The optimal extent of sectioning is not fully understood (Jea et al., 2008). A partial callosotomy involves sectioning of the anterior two thirds of the corpus callosum from the border of the anterior commissure up to the splenium. Sparing the splenium is thought to reduce the risk of disconnection syndromes. A complete callosotomy is carried through the splenium to the arachnoid of the quadrigeminal cistern.

1.4.2 Vagus nerve stimulation

Vagus nerve stimulation (VNS) is an adjunctive treatment in the management of medically refractory epilepsy in patients who are unsuitable candidates for resective surgery. The mechanism of action is not completely understood, although current evidence points towards a deactivation of the nucleus of the solitary tract, with widespread projections to the dorsal raphe nucleus, locus coeruleus, hypothalamus, thalamus, amygdala and hippocampus (Fornai et al., 2011).
A left-sided incision is made in a skin crease in the neck at the mid-cervical level. The approach is similar to that for the anterior cervical discectomy, with the opening of the platysma muscle and development of a plane medial to the sternocleidomastoid muscle. The dissection is then taken more laterally underneath the sternocleidomastoid muscle to expose and open the carotid sheath. The vagus nerve is usually identified in a deep groove between the carotid artery and the jugular vein, and 3-4cm length is exposed. A subcutaneous pocket for the stimulator above the fascia of the pectoralis muscle is created via a horizontal skin incision below the clavicle. An electrode lead is passed between the two incisions, and the helical electrode placed around the vagus nerve. The lead is attached to the stimulator, and the construct is tested. At this point the anaesthetic team should be notified, as there have been reports of cardiac dysrhythmias including asystole during testing (Mapstone, 2008). The stimulator is then placed inside the subcutaneous pocket, and the construct is secured.
2 Outcomes of epilepsy surgery

2.1 Risk benefit analysis

When any surgical procedure is considered, the clinician and patient must consider the anticipated benefits of the procedure, and weigh that against the possible risks. This risk-benefit analysis forms the cornerstone of the decision-making process on whether to proceed to surgery.

Risk benefit analysis in epilepsy surgery is complex. Outcomes may be classified into the following groups.

1. Seizure control
2. Surgical morbidity and mortality
3. Neuropsychological
4. Social

Although many studies have reported on outcomes following epilepsy surgery, there are few rigorous reports (see chapter 1.2.2). Furthermore, the heterogeneity of the population group in terms of pathology, functional status, surgery type and goals of treatment make any group comparison difficult.

For this reason, any risk-benefit analysis has to be tailored to an individual patient, taking into account the aspirations of the patient and their carers, and incorporating a multidisciplinary and holistic approach to their management. This is especially true as the threshold for epilepsy surgery changes, with increased demand in those less severely affected. The question of what constitutes a success in epilepsy surgery varies from one individual to the next, and is perhaps best considered with validated Quality of Life assessments.
2.2 Limitations with previous studies

There have been many studies reporting outcomes following epilepsy surgery. Corroboration between these is limited by differences in informational input and output, and differences in methodology.

<table>
<thead>
<tr>
<th>Input</th>
<th>Heterogeneity in patient age at time of treatment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Heterogeneity in pathology</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity in surgery type</td>
</tr>
<tr>
<td>Methodology</td>
<td>Method of follow up (clinical notes/interview vs self-returned questionnaire)</td>
</tr>
<tr>
<td></td>
<td>Definition of seizure freedom (at time of follow up versus continuous)</td>
</tr>
<tr>
<td></td>
<td>Continuation of anticonvulsants</td>
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<tr>
<td>Output</td>
<td>Length of follow up</td>
</tr>
<tr>
<td></td>
<td>Outcome classification method</td>
</tr>
<tr>
<td></td>
<td>Loss to follow up</td>
</tr>
</tbody>
</table>

*Table 2-1 Heterogeneity in previous studies reporting on outcomes in epilepsy surgery*

2.2.1 Outcome classification scores

The Engel classification system, devised in 1987, is the most commonly used scale (Engel et al., 1993).
<table>
<thead>
<tr>
<th>Outcome Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Free of disabling seizures (excludes early postoperative seizures in first few weeks)</td>
</tr>
<tr>
<td>A</td>
<td>Completely seizure free since surgery</td>
</tr>
<tr>
<td>B</td>
<td>Non disabling simple partial seizures only since surgery</td>
</tr>
<tr>
<td>C</td>
<td>Some disabling seizures after surgery, but free of disabling seizures for at least 2 years</td>
</tr>
<tr>
<td>D</td>
<td>Generalised convulsions with antiepileptic drug (AED) discontinuation only</td>
</tr>
<tr>
<td>Class II</td>
<td>Rare disabling seizures (almost seizure free)</td>
</tr>
<tr>
<td>A</td>
<td>Initially free of disabling seizures but has rare seizures now</td>
</tr>
<tr>
<td>B</td>
<td>Rare disabling seizures since surgery</td>
</tr>
<tr>
<td>C</td>
<td>More than rare disabling seizures since surgery but seizures for the last 2 years</td>
</tr>
<tr>
<td>D</td>
<td>Nocturnal seizures only</td>
</tr>
<tr>
<td>Class III</td>
<td>Worthwhile improvement</td>
</tr>
<tr>
<td>A</td>
<td>Worthwhile seizure reduction</td>
</tr>
<tr>
<td>B</td>
<td>Prolonged seizure-free intervals amounting to greater than the followed-up period but not over less than 2 years</td>
</tr>
<tr>
<td>Class IV</td>
<td>No worthwhile improvement</td>
</tr>
<tr>
<td>A</td>
<td>Significant seizure reduction</td>
</tr>
<tr>
<td>B</td>
<td>No appreciable change</td>
</tr>
<tr>
<td>C</td>
<td>Seizures worsen</td>
</tr>
</tbody>
</table>

Table 2-2 Engel Classification for outcomes for Epilepsy Surgery
The main disadvantage with this classification system is the ambiguity of the term, ‘worthwhile improvement’. This introduces a degree of subjectivity to the classification, making distinction between class III and class IV outcomes, and comparison between different centres difficult.

In view of this and other criticisms, the International League Against Epilepsy (ILAE) proposed a new classification system in 2001 (Wieser et al., 2001). There is good inter-rater reliability between these two different classification systems (Durnford et al., 2011).

<table>
<thead>
<tr>
<th>Outcome Classification</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Completely seizure-free; no auras</td>
</tr>
<tr>
<td>2</td>
<td>Only auras; no other seizures</td>
</tr>
<tr>
<td>3</td>
<td>One to three seizure days per year; +- auras</td>
</tr>
<tr>
<td>4</td>
<td>Four seizure days per year to 50% reduction of baseline seizure days; +- auras</td>
</tr>
<tr>
<td>5</td>
<td>Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +- auras</td>
</tr>
<tr>
<td>6</td>
<td>More than 100% increase of baseline seizure days; +- auras</td>
</tr>
</tbody>
</table>

Table 2-3 ILAE classification for outcomes for Epilepsy Surgery

NB. A seizure day is a 24 hour period with one or more seizures. This may include an episode of status epilepticus.

2.2.2 Temporal lobe surgery

A robust cohort study for 615 patients treated at a single centre with prospective annual follow up for a median of 8 years provides the clearest picture of patterns of seizure remission and relapse following surgery (De Tisi et al., 2011). The Kaplan Meier curves for time to first seizure, according to operation type, is shown below.
Five years after surgery, the seizure-free rates (excluding simple partial seizures) were 55% for ATLR and 56% for temporal lesionectomies.

With ATLRs, the outcome was seen to be associated with pathological changes found at surgery. Patients with focal cortical dysplasia or no detected abnormality had significantly earlier relapses than those with hippocampal sclerosis or DNET. Other studies have similarly reported more favourable outcomes for ATLR with hippocampal sclerosis, although the rates of seizure freedom vary widely (Dunlea et al., 2010, Paglioli et al., 2004, Cohen-Gadol et al., 2006). The best prognostic factors for ATLR appear to be unilateral hippocampal sclerosis in the presence of concordant interictal epileptiform discharges. In one series this gave a seizure freedom rate of 90% at 1 year (Jeong et al., 1999).

The method of ATLR did not affect the outcome in this cohort. There are reports in the literature of the selective amygdalohippocampectomy being associated with lower rates of
seizure freedom (Clusmann et al., 2004). This is likely to be due to poor patient selection, with inaccurate localisation of the epilepsy focus to the mesial structures alone.

For equivalent pathological changes (glioma, DNET, cavernoma, focal cortical dysplasia) outcome was the same between temporal lesionectomy and ATLR.

A meta-analysis comparing outcomes in lesional and nonlesional epilepsy found that the odds of being seizure free following temporal lobe surgery were 2.7 times higher if a lesion was identified and resected (Tellez-Zenteno et al., 2010).

In summary then, outcomes with temporal lobe surgery are most favourable with hippocampal sclerosis, and least favourable when no lesion is identified.

In the de Tisi cohort, 296 patients who underwent ATLRs were seizure free at 2 years. Interestingly the patients who had simple partial seizures in this time were significantly more likely to suffer with long-term seizure relapses than those who did not. This may prove useful in the future to clinicians advising post-operative patients on the risks of AED tapering or cessation.

![Kaplan Meier curve](image)

**Figure 2-2** Kaplan Meier curve to show time to first seizure after temporal lobe surgery in people who had no seizures at all, or who had simple partial seizures only in the first 2 years
(SPS- simple partial seizures)
(De Tisi et al., 2011)

2.2.3 Extratemporal surgery

The rates for seizure freedom in extratemporal epilepsy surgery vary widely in the literature, and the studies have several limitations (see chapter 1.2.2). However, there is a general consensus that outcome is poorer than in temporal epilepsy surgery, as demonstrated by the Kaplan Meier curve in the de Tisi cohort.

It is also well established that extratemporal lesionectomies have better outcomes than nonlesional cases (Janszky et al., 2000), with the odds of being seizure free 2.9 times higher in those with lesions (Tellez-Zenteno et al., 2010). With advances in imaging some previous nonlesional cases can now be reclassed as lesional, with improved projected outcome following surgery. There is little evidence to show significant differences in frontal, parietal or occipital resections, although there are no large studies to adequately address this. However, completeness of resection is an important prognostic factor (Wyllie et al., 1987).

Low grade gliomas and focal cortical dysplasia can have indistinct borders and often encroach on functional cortex (e.g., motor cortex), making for less complete resections and poorer outcomes. The use of cortical mapping or intra-operative mapping during awake craniotomy, is indicated in these cases (Duncan, 2011).

Extratemporal epilepsy is perhaps the most challenging field of epilepsy surgery, and outcome relies most heavily on the pre-operative work-up of patients, concordance between investigations, identification of a structural lesion and complete resection.

2.2.4 Hemispherotomy

Seizure outcome following hemispherotomy is generally very good, as demonstrated in the de Tisi cohort. The procedure is performed for a wide range of pathologies, and outcome is dependent on seizure aetiology. Patients with Rasmussen syndrome, Sturge-Weber syndrome and infantile hemiplegia have better seizure outcomes than those with multilobar
dysplasia or hemimegencephaly (De Ribaupierre and Delalande, 2008). Surgical technique does not seem to be a factor in rates of seizure freedom.

Seizure control is especially important in this group of patients, as better control appears to be related to improved postoperative development.

2.2.5 Palliative

MST is most often employed as an adjunct to cortical resection when functional cortex is encountered. In patients where ‘pure MST’ has been performed, the results are disappointing, with 10% achieving satisfactory seizure control, defined as Engel Class I and II (Schramm et al., 2002).

Corpus callosotomy is well established in the treatment of severe epilepsy with ‘drop attacks’. Long-term atonic seizure control is achieved in over 80% of patients (Jea et al., 2008). Seizure outcome is slightly poorer with partial callosotomy, and some patients require re-operation with complete disconnection to achieve better seizure control.

VNS is now the most common palliative procedure for improvements in seizure control. Overall approximately half of the patients undergoing VNS experience a 50% reduction in the frequency of disabling seizures. It is not yet known how to identify the subset of patients who are most likely to respond to this treatment.

2.2.6 Summary

Seizure freedom is a difficult endpoint to measure, since it is a continuous variable that may change at any point in the patients’ post–operative life, and can only be captured by longitudinal studies with long follow up. Furthermore, seizure pattern may be considered an equally important endpoint; the patient with one seizure 6 weeks after surgery and seizure free since is arguably favourable to a patient seizure free for 2 years but then relapsing with intractable epilepsy.
Late recurrence is not a rare event, with one study quoting a rate of over 60% recurrence at 10 years follow up (McIntosh et al., 2004). Perhaps one question to be addressed is why, despite advances in imaging and other diagnostic tools, there remain a significant proportion of patients who do not respond to surgery? One hypothesis is that the treating teams are lowering their thresholds for treatment, offering surgery to more complex cases with associated lower chances of success. An alternative explanation is that there is a stubborn cohort of patients who have pre-operative concordant investigations, but in fact have a concealed, more generalised epilepsy syndrome.

2.3 Surgical morbidity and mortality

For the purposes of this discussion, surgical morbidity and mortality refers to general and neurological complications that arise from surgery, excluding neuropsychological effects. These will be dealt with separately in chapter 2.4.

2.3.1 Temporal lobe surgery

General postoperative risks include postoperative haematoma and infection. This risk is the same for any surgical group, and most centres report a 1% risk for each. The two main risks for neurological deficit are a visual field defect and a hemiparesis.

The acquired visual field defect is typically a contralateral superior quadrantanopia, caused by injury to the anterior aspect of the optic radiation (Meyer’s loop) during the approach to the temporal horn. The anatomical position of Meyer’s loop shows significant variation between subjects (Nilsson et al., 2007). A study of 24 adult patients showed a quadrantanopia rate of approximately 46% with a rate of failing to achieve UK driving criteria in 25% (Manji and Plant, 2000). The optic radiation can be accurately delineated by tractography, and propagating accurate preoperative tractography onto intraoperative imaging has been shown to reduce the risk of visual defects (Winston et al., 2014).
remains unclear whether similar results can be achieved without the need for intraoperative MRI.

Hemiparesis can be caused by damage to the vascular supply of the basal ganglia, either at the level of the branches of the middle cerebral artery, the anterior choroidal artery or the perforating branches to the brainstem. The risk of temporary hemiparesis is reported in the literature as between 1-2%, and is less than 1% for permanent deficits (Harkness, 2006). This risk can be minimised by good surgical technique. One review advocates against the use of fixed retractors, and strongly supports meticulous subpial resection (Harkness, 2006).

2.3.2 Extratemporal surgery

Surgical morbidity in extratemporal surgery should incorporate the cumulative risks of intracranial recording and any subsequent resection.

The risks of infection and post-operative haematoma during a period of intracranial recording are intuitively greater than for standard surgery. Subdural grids represent a foreign body chronically irritating the cortical surface, and with a clear communication to the outside world. StereoEEG (SEEG) represents the passage of multiple electrodes through the cortical surface and into the deep structures of the brain, with considerable potential for haemorrhage.

Many centres have published their own cumulative complication rates from intracranial subdural monitoring and subsequent resection (Van Gompel et al., 2008, Engel et al., 2003). One large series reported an overall complication rate of 26%, with an infection rate of 12% (Hamer et al., 2002). In general, the literature reports an infection rate of 3-4% and a symptomatic post-operative haematoma rate of 4-5%. The risk of a permanent neurological deficit is reported as 1-2%. The risk of complication increases with duration of intracranial monitoring and number of grids (Hamer et al., 2002).
Implantation of depth electrodes with intra-operative neuronavigation is well established (see chapter 5). In several European centres there is a long tradition of using multiple precisely targeted electrodes in preference to subdural grids. One large series in Milan reported on 215 procedures in 211 patients (Cossu et al., 2005). They reported a complication rate of 5.6%. The most common complication was haemorrhage at 4.2%, although this included asymptomatic bleeds. The rate of clinically significant intracranial haemorrhage, requiring emergency evacuation and leading to permanent neurological deficit, was much lower at 1%.

Surgical complications of extratemporal resections are related primarily to the proximity to eloquent cortex. The primary motor and sensory cortex, and the dominant hemisphere peri-Sylvian areas that subserve speech, are generally considered off-limits. The supplementary motor area (SMA) represents an interesting area where resections can produce profound initial deficits that resolve over the course of 2-3 weeks. Resections can therefore be performed, although pre-operative counselling regarding likely transient deficits is important. In practice, resection boundaries very often encroach close to or into eloquent areas. Safe boundaries of resection can be explored using cortical mapping and awake craniotomy. The overall risk of neurological deficit is very much calculated on a case by case basis, and partially dependent on the degree of caution employed by the surgeon.

2.3.3 Hemispherotomy

The evolution of the modern hemispherotomy was driven by the unacceptably high rate of surgical complications, namely haemosiderosis. The main surgical complications today are hemiparesis and hydrocephalus.

Hemiparesis is very common following hemispherotomy, although a significant proportion of children undergoing the procedure have pre-operative deficits. In one case series in which the authors studied quality of life after hemispherotomy, 84% of the children were able to
walk either alone or with help, and all children who were able to walk before surgery retained the ability to walk well (Delalande et al., 2007).

Acquired hydrocephalus, requiring permanent cerebrospinal fluid (CSF) drainage via shunt placement, is reported in the literature as occurring in 2-16% of cases.

The modern hemispherotomy involves a smaller incision, and is therefore associated with lower rates of blood loss, operation duration and infection. However it remains a large surgical undertaking, and mortality rates range from 4-7% in case series (De Ribaupierre and Delalande, 2008).

2.3.4 Palliative procedures

Complete corpus callosotomy can be associated with callosal disconnection syndromes, although this is usually transient in nature if performed before puberty. Features include intermanual conflict, verbal anosmia, double hemianopsia, and unilateral apraxia and agraphia. Other surgical complications can arise from injuries to structures during the surgical approach, including the superior saggital sinus, pericallosal arteries and the fornix, and prolonged retraction of the hemisphere, leading to hemispheric oedema.

The most common complication arising from VNS insertion is infection, which occurs in up to 5-7% of patients, and usually necessitates explantation. The most common neurological problem is injury to the recurrent laryngeal nerve, leading to vocal cord paralysis. A transient deficit occurs in 4% of patients, and a permanent deficit occurs in 1%.

2.4 Neuropsychological outcomes

Ever since Scoville and Milner’s 1957 milestone report of recent memory loss after bilateral hippocampal lesioning in patient HM (Scoville and Milner, 1957), there has been great interest in the neuropsychological outcomes following temporal lobe surgery. There has been comparatively less research on outcomes following extratemporal surgery, and most of the discussion will therefore focus on temporal lobe surgery.
There are several difficulties with examining the literature on neuropsychological outcomes. Firstly, most of the literature consists of group data, with the potential to mask individual outcomes by combining the proportion of patients who improved, declined and showed no change following surgery. Secondly, individual outcomes may fluctuate with seizure control and anticonvulsant therapy, and may exhibit progressive changes over time. Thirdly, there are a range of methods for assessing outcome, and comparison from one to another introduces a degree of error.

A systemic review of neuropsychological studies providing pooled estimates for different neuropsychological functions was published in 2011, and provides an excellent analysis of current knowledge (Sherman et al., 2011b).

2.4.1 Memory

Memory can be classified in a number of ways, including by timing (long versus short-term), and by type (declarative versus procedural) (Ullman, 2004). The effect of ATLR has been extensively studied with regards to declarative memory in the verbal and visual domains (Helmstaedter et al., 1997, Helmstaedter, 2004).

Verbal memory refers to memory of words and other abstractions involving language. Visual memory refers to perceptual processing, and the encoding, storage and retrieval of those processes. It is well recognised that verbal and visual memory are not equally represented between the temporal lobes, and determining the laterality of different types of memory is of utmost importance prior to surgery. ATLR can worsen both types of memory, by removal of healthy functioning tissue, and can improve both types of memory, by seizure control, cessation of medications and recovery of temporal lobe function (Sherman et al., 2011a).

Pooled estimates of verbal memory demonstrate a decline in 44% of patients undergoing left ATLR, compared with 20% of patients undergoing right ATLR. Gains in verbal memory are
relatively rare, occurring in 7% of left ATLR patients and 14% of right ATLR patients (Sherman et al., 2011b).

Pooled estimates of visual memory demonstrate a similar decline in 21-23% of patients undergoing left and right ATLRs. Gains in visual memory are slightly less common, occurring in 15% of left ATLR patients and 10% of right ATLR patients (Sherman et al., 2011b).

There is some evidence that patients with better baseline performance show greater losses than patients with poor baseline performance, but those who are better preoperatively nevertheless remain better postoperatively. There is also evidence that age at the time of surgery is an important predictor of memory outcome, with a young age associated with increased plasticity and recovery of function (Sherman et al., 2011b).

Currently there is no convincing evidence that the selective amygdalohippocampectomy is associated with improved memory outcomes when compared with the standard ATLR (Adada, 2008, Beaton et al., 2012, Olivier, 2000, Spencer and Burchiel, 2012).

2.4.2 Language

Lateralisation of language function is another important consideration in temporal lobe surgery. Pooled estimates of naming outcomes demonstrate a decline in 34% patients undergoing left ATLR (Sherman et al., 2011b). There is little in the literature on outcomes following right ATLR.

2.4.3 Cognition

Objective measures of cognition such as IQ, executive functioning and attention have shown no significant change following temporal lobe surgery (Baxendale, 2008). Self-reported subjective declines in cognition are also uncommon, with an average of 9% of patients reporting losses and twice as many reporting gains.

2.4.4 Psychiatric

58
Population studies have shown that patients with epilepsy have a higher prevalence of lifetime psychiatric disorders (35%) than the general population (20.7%) (Cleary et al., 2013, Cleary et al., 2012). The most frequent conditions are mood and anxiety disorders, although schizophrenia and other psychoses are also common. The relationship between epilepsy and psychiatric illness is now thought to be bidirectional, and there is great interest in investigating the underlying causes for this.

There are few prospective well controlled studies examining prevalence and severity of psychiatric conditions in the context of epilepsy surgery, using established psychiatric diagnostic criteria. One systematic review of the literature has demonstrated either improvements in psychiatric problems postsurgery or equivalent rates of psychiatric issues postsurgery (Macrodimitris et al., 2011a). The two main predictors of psychiatric outcomes are seizure freedom and presurgical psychiatric morbidity. De novo psychiatric problems are well recognised (1.1-18.2% cases); they are most common in the context of continued seizures and surgical complications.

With regard to major depression, there are high rates in patients before and after undergoing epilepsy surgery (Wrench et al., 2011). The aetiology of this is likely to be multifactorial. Risk factors for post-operative depression appear to include preoperative history, poor postoperative family dynamics and the use of levetiracetam (Barbieri et al., 2015). The majority of cases occur in the first 3 months and persist for at least 6 months. This highlights the need for thorough assessment and diagnosis prior to surgery, and close follow up afterwards.

The presence of psychogenic seizures is no longer a contra-indication to surgery, although it is important to recognise that these patients tend to have worse outcomes with regards to epileptiform and non-epileptiform seizure freedom (Whitehead et al., 2015).

2.4.5 Social outcomes
Measuring quality of life (QOL) is perhaps the most salient endpoint with respect to individual patient outcome. QOL captures the surgical trade-off between improvements in seizure control, and any surgical morbidity or changes in memory and language. There is good evidence that in carefully selected patient groups, satisfaction rates are high following epilepsy surgery (Macrodimitris et al., 2011b). Overall rates of satisfaction are reported at 71%. 64% of patients consider the surgery a success, 78% feel it had a positive effect and 87% would repeat surgery. In this study the most common predictor of satisfaction following surgery was seizure freedom, whereas the most common predictor of dissatisfaction was neurological deficit. Other studies have found that good pre-operative psychological function is another strong determinant for post-operative satisfaction.

Seizure freedom is clearly the most important post-operative determinant of patient satisfaction, since it opens up social opportunities that were previously perceived to be closed, and can free patients from the social isolation they sometimes feel. Indeed, when questioned patients report their own goals from surgery to be driven by social progress, citing employment, driving, independence, socialising and freedom from drugs (Taylor et al., 2001). Significant improvements in full time employment and the ability to drive have been documented following surgery. Patients also perceive general improvements in relationships, independence and overall lifestyle post-surgery, although no objective changes have been observed in marital status, financial status or education (Hamiwka et al., 2011).

However, seizure freedom is not an absolute guarantee for patient satisfaction. There remains a subset of patients who undergo surgery, with good outcomes in terms of seizure freedom with no complications, who nevertheless do not experience a significant improvement in QOL. This is the so-called ‘burden of normality’, where patients are freed from their seizures, but are left ill-equipped to deal with their changing circumstances in terms of self-concept, activities, mood and family dynamics (Wilson et al., 2007).
# 3 Presurgical evaluation of epilepsy

## 3.1 Aims of evaluation

Six cortical zones have been defined in the presurgical evaluation of patients for epilepsy surgery (Rosenow and Luders, 2001). These are listed in the table below.

<table>
<thead>
<tr>
<th><strong>Epileptogenic zone</strong></th>
<th>Region of cortex that can generate epileptic seizures. By definition, total removal or disconnection is necessary for seizure freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irritative zone</strong></td>
<td>Region of cortex that generates interictal epileptiform discharges, evident in the EEG or magnetoencephalography (MEG)</td>
</tr>
<tr>
<td><strong>Seizure onset zone</strong></td>
<td>Region where the clinical seizures originate</td>
</tr>
<tr>
<td><strong>Epileptogenic lesion</strong></td>
<td>Structural lesion that is causally related to the epilepsy</td>
</tr>
<tr>
<td><strong>Ictal symptomatogenic zone</strong></td>
<td>Region of cortex that generates the initial seizure symptoms</td>
</tr>
<tr>
<td><strong>Functional deficit zone</strong></td>
<td>Region of cortex that in the interictal period is functionally abnormal, as indicated by neurological examination,</td>
</tr>
<tr>
<td></td>
<td>neuropsychological testing and functional imaging or non-epileptiform EEG or MEG abnormalities</td>
</tr>
<tr>
<td><strong>Eloquent cortex</strong></td>
<td>Region of cortex that is indispensable for defined cortical functions</td>
</tr>
</tbody>
</table>

*Table 3-1 Description of cortical zone and lesions (Rosenow and Luders, 2001).*

The epileptogenic zone is defined as the area of cortex indispensable for the generation of clinical seizures. It may include the actual epileptogenic zone, which is the cortical area generating seizures before surgery, and a potential epileptogenic zone, which may later
generate seizures after resection of the presurgical seizure onset zone. There is no single diagnostic test for the epileptogenic zone, and it can only be identified retrospectively, with long-term seizure freedom following cortical resection. The aim of presurgical evaluation is to infer the localisation of the epileptogenic zone, and ensure that this can be safely resected without causing significant deficits. There are a wide range of diagnostic modalities that define the other five cortical zones. In an ideal surgical candidate there would be a large degree of overlap between these zones, and a cortical resection would carry a high chance of seizure freedom. However, in most patients there is some discordance between zones in location and extent, and the significance of each has to be carefully weighted. Determining the contribution of each zone to the putative epileptogenic zone is challenging, and requires a multidisciplinary approach with input from neurophysiologists, neuroradiologists and neurologists.

![Illustration of discordant cortical zones and lesions](image)

**Figure 3-1 Illustration of discordant cortical zones and lesions**

3.2 Patient selection

There are four general criteria necessary for patients to meet to be considered candidates for presurgical evaluation and resective surgery.
1) Drug resistant epilepsy
2) Clinical diagnosis of focal seizures
3) Absence of contra-indications for presurgical evaluation and epilepsy surgery
4) Declaration by the informed patient and/or carer that he/she wishes to undergo presurgical evaluation

Patients who suffer with additional psychogenic seizures may still be considered for surgery, although there is a considerable risk for worsening psychiatric morbidity (Whitehead et al., 2015). Patients with reduced levels of intelligence are no longer excluded from presurgical evaluation, with the goal of surgery to improve quality of life and ease of care.

3.3 General pathway for presurgical evaluation

Presurgical evaluation aims to propose a hypothesis on the localisation of the epileptogenic zone. The general pathway followed by most Epilepsy Surgery Units is described below.
Figure 3-2 The common pathways for presurgical evaluation in epilepsy surgery (Duncan, 2011).

The initial clinical evaluation and clinical investigations are commonly referred to as Phase I in the process (Herskovitz and Schiller, 2016), and are described in detail in this chapter. If the outcome of Phase I is a clear hypothesis for the site of the epileptogenic zone, in an area that is surgically accessible with concordant investigations, then the recommendation may be to proceed with resective surgery. If there is uncertainty on the localisation of the
epileptogenic zone, further investigations are often necessary and may include a period of intracranial EEG (Duncan, 2011). This is known as Phase 1.5, and will be discussed more in chapter 4.3.

3.4 Clinical evaluation

Clinical evaluation takes the form of a formal history and examination of the patient by a Neurologist specialising in epilepsy.

The history should be taken from the patient and also family or friends who have witnessed the seizures. A good history of seizure pattern and semiology is important in ascertaining that the seizure is focal, and inferring site of the seizure onset. The first manifestations of the seizure are most important in localising the symptomatogenic zone, and there are several manifestations that provide reliable lateralising signs.

Seizure semiology is classified into the following broad groups (Luders et al., 1998). Seizure semiology is inferred from both the history given by the patient, and the independent review of seizure morphology from scalp EEG-video telemetry.

<table>
<thead>
<tr>
<th>Semiology type</th>
<th>Description (ictal manifestations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td>Sensory, psychosensory and experiential symptoms</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Objectively documented autonomic alterations</td>
</tr>
<tr>
<td>Dialeptic</td>
<td>Alteration of consciousness independent of ictal EEG manifestations</td>
</tr>
<tr>
<td>Motor</td>
<td>Mainly motor symptoms. Can be simple or complex depending on type of movements</td>
</tr>
<tr>
<td>Special</td>
<td>Characterised by negative features (atonic, astatic, hypomotor, akinetic, aphasic)</td>
</tr>
</tbody>
</table>

*Table 3-2 Seizure semiology classification (Luders et al., 1998)*
A thorough past medical history, including pregnancy, birth and childhood histories, is useful in detecting antecedent predisposing factors in epilepsy. Specifically a patient may report delayed developmental milestones, or a history of meningitis, encephalitis, head injuries or febrile convulsions.

A drug history is required to ensure the patient has undergone a reasonable trial of medical treatment. Drug resistant epilepsy is defined by most units as two years of seizures, not controlled by two first line drug treatments tried at the maximal tolerated dose. In fact it is now known that failure to respond to one drug treatment is a good predictor for refractory epilepsy (Kwan and Brodie, 2000).

A social history allows the neurologist to ascertain whether the seizures can be classed as debilitating. This is a subjective term and not necessarily related to seizure frequency. Common uncontrolled seizures clearly interfere with social development and the ability to form relationships and gain employment. However, even rare seizures can inflict psychological morbidity, affect employment and driving, and the side effects of medications can be poorly tolerated.

A thorough examination of the cardiovascular, respiratory, gastro-intestinal and neurological system and skin is undertaken, to ensure general fitness to proceed, and to document any established deficits or associated conditions.

Finally it is important to have a discussion with the patient regarding their goals for surgery, and whether this is realistic in their case.

3.5 Scalp EEG and video telemetry

3.5.1 Background

EEG is the recording of the brain’s spontaneous electrical activity, and is the fundamental technique in identifying the irritative zone and the ictal onset zone. Scalp EEG is carried out
as an inpatient in association with simultaneous video recording, which allows corroboration of the change in electrical activity with a reliable real time recording of the evolving seizure semiology. Scalp EEG and video telemetry is time and labour-intensive, and is a limited clinical resource. It is performed in specialised telemetry units, with staff trained in the recognition of subtle seizure activity and seizure management. The duration of the recording and the withdrawal of anticonvulsants are tailored to individual patients.

The specific uses of EEG in presurgical evaluation for epilepsy include:

- Ensuring that the individual has epileptic seizures (4-10% of patients in surgical programs have co-morbid psychogenic non-epileptic seizures)
- Characterisation of electro-clinical seizure features, and show concordance with other data
- Demonstration of epileptogenicity in the presumed pathological substrate of refractory epilepsy
- Identification of other epileptogenic foci

3.5.2 Epileptiform discharges

The normal EEG is asynchronous. Focal epileptiform phenomena consist of spike discharges, spike or polyspike wave complexes and sharp waves. They evolve from the background rhythm and occur in a discrete area of the brain.

- Sharp wave: transient, clearly distinguishable from background activity, with pointed peak and duration of 70-200ms
- Spike: Similar to sharp wave, with duration of 20-70ms
- Spike wave complexes: spike followed by slow wave, with slow wave being of higher amplitude than spike
- Polyspike and wave complex: 2 or more spikes associated with 1 or more slow waves
- Normal or nonspecific sharp transients

Epileptiform discharges must be distinguished from normal or nonspecific sharply contoured waveforms, which do not represent epileptiform activity. These can be divided into physiological transients, stereotyped normal EEG variants and nonspecific waveforms.

3.5.3 Ictal EEG

Ictal discharges are most useful in localising seizure onset zone within the first 30 seconds of seizure onset. Localisation of the seizure is usually straightforward using the standard 10-20 system of electrode placement, with additional electrodes for the anterior temporal lobe (inferior sphenoidal electrodes.) Localised and lateralised changes are most likely in temporal lobe epilepsy, and epileptiform or high frequency discharges are most likely in superficial neocortical epilepsy. Frontal lobe epilepsy often shows generalised or widespread high frequency activity, slow rhythms and attenuation as a result of rapid propagation or secondary generalisation.

There are several limitations with ictal EEG. Firstly, scalp EEG is prone to contamination with artefacts, and significant muscle artefact often obscures the brain’s electrical activity during a seizure. Secondly, in cases where the epileptogenic zone is small, circumscribed and remote to electrodes, the ictal discharges may not be detected at all. Finally, some patients have infrequent seizures, and it can be difficult to capture ictal activity despite long-term recording and provocation measures.

3.5.4 Interictal EEG

Interictal discharges represent areas of cortical irritability that may be predisposed to epileptiform activity, ie the irritative zone. Consistent localisation of the irritative zone by multiple recordings over a period of time is a good marker for reliability. However, the volume of cortex that needs to be excited prior to scalp EEG recording means that most interictal activity is not detected. Also, as previously discussed the EEG of normal subjects
may show a range of spikey features, or non-epileptogenic variants, that can complicate EEG interpretation.

3.5.5 Quantitative EEG
Quantitative EEG is the mathematical processing of digitally recorded EEG (Nuwer, 1997). Applications include signal analysis, automated event detection, monitoring and trending EEG, source analysis and frequency analysis. The potential advantages of this technique are considerable, although the technology has not advanced sufficiently for use in regular clinical practice. The main disadvantage of quantitative EEG is that it cannot take into account variables such as patient age, state of alertness and medication, leading to high rates of ‘false-positives’.

3.5.6 Seizure semiology
Independent review of evolving seizure semiology is important in defining the symptomatogenic zone. Video telemetry allows careful examination of seizure semiology, including aura. Rapid, targeted examination of the patient is crucial to extract the most information possible, such as impairment of consciousness, speech and comprehension, and memory, motor, sensory and visual function.

Since most of the human cortex is ‘silent’ when stimulated, the symptomatogenic zone may not overlap with the epileptogenic zone. Instead it often neighbours the epileptogenic zone, and produces the clinical signs of seizure semiology following local spread and activation.

3.6 Structural imaging
The workhorse imaging technique in the presurgical evaluation of epilepsy is the Magnetic Resonance Imaging (MRI) scan, which was first introduced into mainstream practice in 1984. MRI has revolutionised Epilepsy Surgery, since the detection of an epileptogenic lesion is associated with significantly better outcomes with regards to seizure freedom
following surgery (Tellez-Zenteno et al., 2010). With modern MRI protocols, 20% of patients with refractory focal epilepsy and previously unremarkable imaging are now found to have a focal lesion (Duncan, 2010). Overall this has reduced the proportion of patients with true MRI-negative epilepsy to 25-40%. It is therefore important to ensure patients have undergone modern imaging protocols before it can be confidently stated that there is no epileptogenic lesion.

Modern epilepsy MRI protocols, supported by automated and quantitative techniques, are described further in chapter 4.

3.7 Neuropsychology

Neuropsychological assessment is an essential component to presurgical evaluation. There are three roles to this assessment (Helmstaedter, 2004).

1. Baseline assessment of presurgical neuropsychology
2. Localisation and lateralisation of epileptic focus
3. Prediction of likely neuropsychological effects of resective surgery

The existence of pre-existing cognitive deficits can reflect irreversible impairments due to lesions and brain damage underlying epilepsy, and reversible impairments due to treatment with AEDs and epileptic dysfunction around or between seizures. To distinguish between these, assessment is best carried out at least 12 hours after the most recent generalised seizure. Despite the negative cognitive effects of AEDs, the risk of seizures following withdrawal means patients are assessed on their medication.

Neuropsychology aids in seizure localisation, as certain localised epilepsies have characteristic cognitive profiles. In temporal lobe epilepsy material-specific memory impairment can indicate lateralised temporal lobe dysfunction. There is a strong association between left temporal lobe epilepsy and impairment of verbal memory, and a less consistent relationship between right temporal lobe and visuospatial memory. A quantitative and
Qualitative differentiation between mesial and lateral left temporal lobe epilepsy can be made via verbal learning and memory assessment (Helmstaedter et al., 1997). Impairment of attention and executive functions occurs with frontal lobe epilepsy, although this is also seen in temporal lobe epilepsy and in clinical practice a frontotemporal dysfunction is common. Localising epilepsies to the parietal and occipital lobes is difficult, with good compensation for the classical parietal symptoms of aphasia, alexia, agraphia, acalculia, agnosia, neglect (Helmstaedter and Lendt, 2001).

Recognition of likely unacceptable neuropsychological deficits from cortical resection is achieved by assessing the functional reserve of the contralateral structures and the lateralisation of speech function. Historically, lateralising function was achieved by the intracarotid amobarbital test, first introduced by Wada at the Montreal Neurological Institute (Wada and Rasmussen, 2007). This involves the catheterisation of the internal carotid artery for each hemisphere, an angiogram and infusion of a short-acting anaesthetic to inactivate one hemisphere, followed by a series of standardised tests for language and memory. It is worth noting that practically all right handed patients have their speech representation in the left hemisphere. Left handed patients without early injury to the left hemisphere have dominance for speech in the left hemisphere in 70% and have bilateral speech representation in 15%. Left handers with early injury to the left hemisphere have speech representation on the left in 30%, bilaterally in 19% and on the right in 51% (Rasmussen and Milner, 1975). There remains controversy over the use of the ‘Wada test’ in assessing memory, as the carotid artery is not an important vascular contribution to the mesial temporal structures in most people. There is also a risk of permanent neurological deficit. Many centres have abandoned this test, in favour of functional MRI (fMRI) and baseline neuropsychological examination to assess language (Baxendale, 2009).
3.8 Neuropsychiatry

There is a well-documented bidirectional relationship between epilepsy and psychiatric illness. Population based studies have shown that patients with epilepsy have a higher prevalence of lifetime psychiatric illness than the general population (35 v 20.7%), with the most common disorders being mood and anxiety disorders (24.4 v 13.2%) (Tellez-Zenteno et al., 2007). There is also increasing recognition that lifetime psychiatric history predicts worse outcomes with regards to seizure freedom following surgery (Kanner et al., 2009).

There is mixed evidence on long term psychiatric outcomes following surgery. A systematic review on the subject published in 2011 demonstrated no long term deterioration in psychiatric outcome (Macrodimitris et al., 2011a), and in fact suggested improvement. However, a more recent retrospective study identified that 38% (105/280) of patients undergoing surgery for temporal lobe epilepsy suffered significant psychiatric problems within 4 years of surgery (Cleary et al., 2012), with 18% of this morbidity thought to be de novo. Risk factors for post-surgical psychiatric disorders may include the presence of presurgical depression, presurgical interictal psychosis and epileptiform discharges contralateral to the epileptogenic zone (Filho et al., 2012) and also failure of surgery to control seizures (Macrodimitris et al., 2011a). The rates of de novo psychiatric conditions are 1.1-18%, with the likelihood inversely related to the seriousness of the psychiatric condition (Macrodimitris et al., 2011a). Psychogenic seizures are seen in 6-8% patients undergoing presurgical evaluation with scalp EEG-video telemetry (Gallego et al., 2011). These may occur as an isolated conversion disorder or may coexist with organic epilepsy. Psychiatric intervention is key to establishing causative factors and treating conversion disorders (LaFrance, 2008). Most centres would consider psychogenic seizures as a powerful negative predictor for a good outcome following surgery (LaFrance, 2008, Whitehead et al., 2015).

There is certainly the need for more prospective well controlled studies, using established psychiatric diagnostic criteria, to record the prevalence of psychiatric disorders and predictors of poor outcome following surgery (Barbieri et al., 2015, Cleary et al., 2013, Cleary
et al., 2012, Filho et al., 2012, Kanner et al., 2009, Wrench et al., 2011). All patients undergoing presurgical evaluation for epilepsy surgery should have a systematic psychiatric or psychological assessment, including both a structured diagnostic interview and a psychometrically sound symptom measures both prior to and following surgery. Since the majority of psychiatric changes occur within the first year of surgery, most assessments should be completed by 1 year after surgery.

3.9 Multi-disciplinary team meeting

The essential components of the Phase I review for presurgical evaluation are the clinical history and examination, scalp EEG with video telemetry, optimal structural imaging, neuropsychology and neuropsychiatry. This data should be presented and integrated at a Multi-Disciplinary Team meeting, involving neurologists, neurosurgeons, neuroradiologists, neurophysiologists and neuropsychologists. If these data are concordant, indicating a single dysfunctional area that may be removed without causing a deficit, and if there is no evidence that the rest of the brain is abnormal, no further investigations are required. If however, there is no structural lesion, or if there is dual pathology or discordant data, then further investigations may be necessary. This includes advanced imaging, and the use of intracranial EEG.
Advanced Investigations in Epilepsy Surgery

4.1 Localising the epileptogenic zone

4.1.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is used to identify the structural basis of epilepsy. The importance of identifying a structural lesion with regard to post-operative seizure outcome has been emphasised elsewhere. In the presurgical evaluation of epilepsy patients, the most sophisticated and comprehensive imaging protocol is therefore indicated.

A typical presurgical MR protocol consists of (Duncan, 2010):

- Volume acquisition T1 weighted data set acquired in oblique coronal orientation, orthogonal to the long axis of the hippocampi, and covering the whole brain in 0.9mm partitions.
- Oblique coronal spin-echo sequence with proton density (TE=30)
- Oblique coronal heavily T2 weighted
- Oblique coronal fluid attenuated inversion recovery (FLAIR) acquisitions

Analysis of the imaging can be done by visual inspection alone, or increasingly by a voxel-based analysis.

The single most common pathology underlying focal seizures is hippocampal sclerosis (HS). The features on MRI of HS are hippocampal atrophy, demonstrated with coronal T1 weighted images, and increased signal intensity within the hippocampus on T2 weighted spin-echo images, decreased T1 weighted signal intensity and disruption of the internal structure of the hippocampus (Jackson et al., 1990). HS is often associated with more widespread changes, including atrophy of temporal lobe grey and white matter, dilatation of the temporal horn and blurring of the margins between grey and white matter. Computational analysis of the three-dimensional shape of the hippocampus has demonstrated distinct and
useful regional distortions associated with HS, which may prove useful in patients with temporal lobe epilepsy and normal conventional MRI (Hogan et al., 2008).

Hippocampal asymmetry of 20% or more is reliably identified by visual inspection by an experienced neuroradiologist. Asymmetry less than 20% is best detected by the quantitative assessment of the hippocampi, a process called manual hippocampal volumetry. This is a time consuming and demanding technique, requiring a skilled operator and a post-processing computer (Duncan, 2010). However, it is useful in identifying subtle hippocampal damage and ensuring the contralateral hippocampus is intact. There are now reliable voxel-based, automated methods of hippocampal volumetry (Bonilha et al., 2009, Winston et al., 2013).

A quantitative assessment can also be made of the hippocampal T2 relaxation time. Regional changes in hippocampal T2 relaxation can be used to lateralise the epilepsy in the absence of other markers. However, this is best used in conjunction with volumetry and morphology, to provide the most complete and refined method for assessment of hippocampi on MR (Woermann et al., 1998).

With advances in structural imaging, previously cryptogenic cortical lesions are increasingly being discovered. This includes schizencephaly, agyria, diffuse and focal macrogyria, focal polymicrogyria, minor gyral abnormalities, subependymal grey matter heterotopias, bilateral subcortical laminar heterotopia, tuberous sclerosis, focal cortical dysplasia (FCD) and DNETs. FCD is not always visible on conventional MRI, and identification may require further processing. This may include sulcal analysis and data reconstruction in curvilinear planes. Voxel-based analyses of signal and texture have also been used to model cortical thickening, blurring of the grey-white matter junction and hyperintensity within the lesion (Bernasconi et al., 2001). Furthermore, novel imaging techniques such as magnetic spectroscopy, magnetisation transfer imaging and diffusion weighted imaging (DWI) can
further improve the sensitivity of detecting a subtle FCD. Despite this, there remain a significant number of FCD lesions that remain undetected with current imaging techniques.

Voxel-based analysis of FLAIR in these patients has been shown to detect abnormalities in 14% of cases, half of which have been concordant with other investigations (Focke et al., 2009).

Cavernomas are easily identified on MRI, with a characteristic appearance of well circumscribed lesions containing blood products. The central part contains areas of high signal on T1 and T2 weighted images, reflecting oxidised haemoglobin, with darker areas on T1 weighted images due to deoxyhaemoglobin. The ring of surrounding haemosiderin appears dark on T2 weighted imaging, and there may be calcification with dark areas on T1 and T2 weighted imaging.

The most common lesions in the developing world are granulomas from cysterciosis and tuberculosis. These have characteristic appearances on MRI which evolve over time. Other lesions that may be identified include trauma and infarction.

4.1.2 Diffusion weighted imaging

DWI is an MRI sequence that measures the diffusivity of water in each voxel. The primary clinical use of DWI is to infer white matter connectivity through tractography. However there is current interest in the use of DWI as a sensitive marker for cryptogenic pathology in epilepsy (Rugg-Gunn et al., 2001). DWI is very sensitive to early ischaemic changes, and shows changes in status epilepticus that likely represent the effects of seizures. More usefully, spatial concordance has been demonstrated between epileptiform activity in patients undergoing SEEG and diffusion abnormalities in DWI (Guye et al., 2007), indicating a potential role in localising the epilepsy focus. In frontal lobe epilepsy, the use of DWI in association with fluorodeoxyglucose positron emission tomography (FDG-PET) was found to
be more efficient at determining the epileptogenic zone than FDG-PET alone (Thivard et al., 2011).

4.1.3 Ictal-interictal subtraction single photon emission CT (SPECT)

SPECT involves the intravenous injection of a radiolabeled tracer, which is then detected by CT and used to infer cerebral blood flow (CBF). The most commonly used tracers are 99mTc-hexamethyl-propylenamine oxime and 99mTc-ethyl cysteinate dimer.

Interictal SPECT is not used alone for presurgical evaluation. The epileptic focus is typically indicated by a region of reduced CBF, but studies have demonstrated very poor reliability (Dasheiff, 1992). Ictal SPECT is far more useful, giving a general pattern of localised hyperperfusion with surrounding hypoperfusion, which is followed by accentuated hypoperfusion in the region of the focus, which gradually returns to the interictal state. This has been used in both temporal lobe and extra-temporal lobe epilepsy. A meta-analysis of published data showed that in patients with temporal lobe epilepsy (TLE), the sensitivities of SPECT relative to diagnostic evaluation were 0.44 (interictal), 0.75 (post-ictal) and 0.97 (ictal) (Devous et al., 1998).

Coregistration of inter-ictal with ictal SPECT images generates an ‘ictal difference image, which highlights the dynamic changes to CBF that occur during seizure activity. This is known as ictal-interictal subtraction SPECT. Coregistration of this image to MRI then places the changes in CBF in an anatomical framework, and is called subtraction ictal SPECT coregistered to MRI (SISCOM). This technique has been found to improve both the accuracy and interpretation of ictal SPECT (O’Brien et al., 1999). A recent study describing the prospective use of subtraction SPECT and SISCOM in 175 patients undergoing presurgical evaluation gives very good results, especially in view of the difficult patient group. Concordance with seizure onset was demonstrated in 82% of those who progressed to resective surgery, and 75% of those who underwent intracranial recording (von Oertzen et al., 2011). In addition, it has been shown that voxel-based analysis of SPECT, specifically of
the difference between ictal and interictal CBF as a Z-score of the interscan variation of SPECT scans, further improves accuracy over just thresholding the subtraction images (Kazemi et al., 2010).

Ictal SPECT is technically challenging since the tracer has to be injected as soon as possible after the seizure starts. The inevitable delay means that any local changes in CBF may reflect seizure propagation more than the seizure onset zone. As a result, subtraction SPECT should be used with a degree of caution and should be performed with simultaneous video-EEG, to determine the exact relationship between seizure onset and tracer delivery. Measures to reduce the time to tracer delivery, including automatic dose injection systems, are currently being trialled (Setoain et al., 2012).

Subtraction SPECT and SISCOM is most commonly used in the presurgical evaluation of patients who have normal MRI scans or who have discordant investigations. Due to the inherent difficulties distinguishing between changes in CBF from seizure onset and seizure propagation, this technique is usually used to help generate a hypothesis, which may then be tested with intracranial electrode recordings.

![Figure 4-1 Inter-ictal, ictal and subtraction SPECT (NHNN records)](image)

**Figure 4-1** Inter-ictal, ictal and subtraction SPECT (NHNN records)

4.1.4 Positron emission tomography (PET)

PET is a further example of functional imaging, using tracers labelled with positron-emitting isotopes to map cerebral glucose metabolism. The tracer used is 18F-deoxyglucose (FDG).
FDG-PET cannot be used to capture the ictal state, since tracer uptake occurs over 40 minutes after injection. Instead FDG-PET is used in the inter-ictal state, and typically demonstrates an area of hypometabolism, which is often more extensive than the epileptogenic focus. The value of the PET data can be enhanced by the voxel-based comparisons of individual scans with normal data (Muzik et al., 2000). PET images can also be coregistered with MRI to provide an anatomical framework for the hypometabolism.

Historically FDG-PET, in association with CT, was the imaging workhouse for epilepsy surgery. In the modern era FDG-PET has no role to play if a structural lesion is seen with concordant video and EEG data. However, in cases with discordant data, unremarkable MRI scans or dual pathology, FDG-PET continues to be important. For example, in some patients, re-review of the original MRI after finding a focal area of hypometabolism can reveal a previously covert structural abnormality (Lee and Salamon, 2009, Rathore et al., 2014).

Like SPECT, FDG-PET is therefore most useful in generating a hypothesis, which can be tested with intracranial EEG. Interestingly the seizure onset zone is often found at the margin of the area of hypometabolism. Since the area of hypometabolism is usually extensive, a tailored resection according to its boundaries is not practical in most cases.

There is great interest in developing specific PET ligands that better identify the epileptogenic zone by binding to occult surgical lesions. For example, both 11C-flumazenil and 11C-alpha-methyl-L-tryptophan (AMT) are thought to bind to occult lesions (Richardson et al., 1998). These could offer a significant improvement compared with FDG-PET in the spatial localisation of the putative epileptogenic zone, and more directly inform subsequent surgical resections. In one study, 25% of children with refractory focal epilepsy and normal MRI had a focal increase in AMT binding, and positive findings had a high specificity for the identification of the epileptogenic focus (Wakamoto et al., 2008). However, in another study 11C-flumazenil was not found to be superior to FDG in the presurgical evaluation of
temporal lobe epilepsy (Debets et al., 1997). Unfortunately the cost and lack of availability of 11C radiochemistry have prevented this from more widespread use in research and clinical practice, and any advances with AMT PET will probably require the development of an 18F-labelled variant. Despite this, the emergence of novel tracers is an exciting prospect for future improvements in presurgical evaluation.

![Figure 4-2 FDG-PET demonstrating right parietal hypometabolism (NHNN records)](image)

4.1.5 EEG-fMRI

EEG-fMRI is the simultaneous recording of EEG and fMRI, to map cerebral blood oxygen level-dependent (BOLD) signal changes associated with interictal (IED) and ictal epileptic discharges. This is a powerful non-invasive technique, combining the high spatial resolution of fMRI with the excellent temporal resolution of EEG. Studies last between 10 to 40 minutes, with a corresponding limit on the positive yield. 50% of adults with refractory focal epilepsy and frequent IEDs will have an IED during EEG-fMRI recording, with 50% of these individuals showing an identifiable BOLD signal change (Gotman et al., 2004).

Electrical source imaging (ESI) is a technique that localises the epileptiform discharges recorded from EEG. The temporal resolution of ESI is sufficient to resolve propagation patterns. In patients with concordant data, maximal BOLD signal and ESI dipoles were found to be <33mm apart (Vulliemoz et al., 2009), indicating reasonable spatial concordance.
EEG-fMRI has been incorporated in a few centres in the presurgical evaluation of patients. Concordance between BOLD signal and electroclinical localisation of the epileptogenic zone is reasonable, at 40-60% (Salek-Haddadi et al., 2006). A new technique, named the Grouiller method, has potential to improve concordance, incorporating voltage maps of epileptic spikes obtained previously into the scanner (Grouiller et al., 2011). Currently, EEG-fMRI remains a research tool, with no clear clinical applications. In a recent study, 76 patients undergoing presurgical evaluation underwent EEG-fMRI, and the locations of the IED BOLD signal were correlated with resection margins and surgical outcome (Thornton et al., 2010). Only 21 had epileptiform discharges recorded, demonstrating the low yield with this technique, and only 10 proceeded to resective surgery. 7 of the 10 were seizure free following surgery, and there was concordance between the BOLD signal and resection in 6 of the 7. In the remaining 3 patients, who continued to suffer with seizures post-operatively, the BOLD signal lay outside the resection zone. This suggests a possible negative predictive value for EEG-fMRI, where lack of concordance predicts poor surgical outcome. More prospective studies are required, using EEG-fMRI for localisation in the presurgical evaluation of patients who proceed to surgery and achieve postoperative surgical freedom.

The feasibility of combining fMRI with intracranial EEG is currently being studied. Intracranial recordings give clearer results, but have limited spatial sampling. Combining this with fMRI, it may be possible to infer whether EEG is recording close or distant to maximal BOLD signal, and seizure onset zone.

4.1.6 Magnetoencephalography (MEG)

MEG is the direct recording of the magnetic brain activity associated with neuronal activity in the cerebral cortex. The neural generators of the MEG and EEG signal are identical, with the majority of the signal arising from the post-synaptic activity in the pyramidal cells of the cerebral cortex. However, there are important differences that make this these two techniques complimentary. MEG selectively detects tangential sources, whilst EEG
preferentially detects radial sources, with an inevitable perturbation of the electrical potentials by overlying structures (Barkley and Baumgartner, 2003). In practice this makes MEG more useful at detecting activity in superficial, non-radial areas of cortex, and in the walls of sulci. This also means that, while EEG provides more comprehensive information, MEG is more amenable to dipole localisation techniques using either standard spherical or individual head shape models.

The magnetic waveforms are recorded by an array of superconducting quantum interference devices (SQUIDS). The localisation of this waveform is mathematically complex. This is known in mathematics as the inverse problem: generally the inverse solution of electromagnetic measurements is non-unique and ill-posed. If proper assumptions are made, however, the solution becomes solvable. There are several methods available to solve the inverse problem and achieve a source localisation.

Clinically MEG can be used for the mapping of eloquent cortex including motor, sensory, language and visual areas (Stufflebeam, 2011).

MEG can also be used in the localisation of the irritative and seizure onset zone in epilepsy. Patients undergo simultaneous EEG and whole head MEG, and both interictal and ictal activity is recorded. MEG has been shown to play an important role in the presurgical evaluation of patients with epilepsy, influencing clinical decision and increasing the likelihood of seizure freedom (Knowlton, 2008).

4.2 Protecting eloquent cortex

4.2.1 Functional MRI

Functional MRI (fMRI) is a technique for mapping areas of function to the cortical surface. It can be used to map language, motor function, memory and epileptic activity. The technique indirectly detects focal areas of increased neuronal activity by identifying increased CBF when the patient performs specific tasks.
Using echo-planar imaging (EPI) sequences, a series of scans of the entire brain are generated, that are sensitive to changes in blood-oxygen-level-dependent (BOLD) signal. The BOLD signal represents the ratio of oxyhaemoglobin concentration to deoxyhaemoglobin. These have different signal characteristics on T2 weighted imaging. A greater concentration of oxyhaemoglobin compared with deoxyhaemoglobin produces a high BOLD signal, and identifies an area with increased neuronal activity as a result of localised hyperperfusion (Gholipour et al., 2007).

A BOLD signal is created for each region of interest during a specific activity, and is then compared with the signal in the same region in the resting state. Signal averaging over multiple acquisitions provides a map of the likelihood that function is present in this area. This signal map is coregistered with conventional MRI to provide spatial, anatomic resolution.

There are a number of limitations to this technique. Firstly the area of BOLD activation is greatly influenced by thresholding, and can be widespread or focal. Secondly, there is no direct relationship between BOLD intensity and cortical eloquence. Thirdly, one cannot assume that areas that do not surpass the chosen threshold are functionally inert. Finally, the area of BOLD activation might not be crucial to the execution of the task, and the task itself may not accurately reflect functional ability.

4.2.1.1 Motor cortex

Many studies have been performed that validate the use of motor fMRI to localise the motor cortex, using direct cortical stimulation as the gold standard. For example, Majos et al compared pre-operative motor fMRI with direct cortical stimulation in 25 patients with peri-Rolandic tumours, and reported an 84% correlation (Majos et al., 2005).

Anatomically the motor cortex and somatosensory cortex lie either side of the central sulcus. However, the arcade of pial membranes and cortical vessels make identification of the
central sulcus by inspection difficult intra-operatively. fMRI incorporated into neuronavigation platforms is useful in giving the surgeon further evidence on gyral functional anatomy.

Motor fMRI is also useful in the identification of regions of interest necessary for generating the corticospinal tractography.

4.2.1.2 Language
The intracarotid amytal test (Wada test) is the traditional gold standard investigation to determine the laterality of language and memory function. However there are two limitations with this technique. Firstly, it is an invasive study, and carries a 0.6% risk of stroke. Secondly, the study is dependent on the internal carotid artery being the sole blood supply to the functional area tested, with no hemispheric cross-over. Increasingly language fMRI is being used to determine the laterality of language dominance.

Expressive language is assessed with verbal fluency and verb generation tests, and receptive language function is assessed with a reading comprehension task. Commonly verbal fluency tests generate stronger and wider activations than verb generation tasks (Sanjuan et al., 2010). Receptive language paradigms commonly show bilateral activation. A degree of functional reorganisation has been observed, with functions close to pathology more likely to relocate contralaterally, and functions distant to pathology more likely to remain in the ipsilateral hemisphere (Berl et al., 2005). Various methods to quantify the lateralisation of BOLD signal have been suggested, including counting the voxels above a set threshold, and determination of the BOLD signal in anatomically defined areas (Bonelli et al., 2012). The most effective measures are those that do not rely on thresholding (Suarez et al., 2009). Most often the lateralisation of function is clear from visual inspection.

Language fMRI shows high levels of concordance with the Wada test in lateralising language function (Woermann et al., 2003). Since it is cheap, non-invasive and repeatable, there are many centres that have abandoned the Wada test in favour of language fMRI for lateralisation of function. However, the use of fMRI to localise language function is less clear.
If a resection close to language cortex is being considered, the critical area should still be mapped through direct stimulation, either with implanted electrodes post-operatively, or in the awake patient at surgery.

4.2.2 Diffusion weighted imaging and tractography

Diffusion weighted imaging (DWI) is an MRI method that maps the diffusion of water in biological tissues, so that each voxel has an intensity that reflects the best measurement of the rate of water diffusion. DWI is used to delineate the white matter pathways of the brain through a technique called tractography (Yamada et al., 2009).

Water diffusion anisotropy (direction) in the white matter is defined by axonal alignment. Water diffuses preferentially in a direction parallel to the longitudinal axis of the axon, and diffusion is restricted perpendicular to the axis. Each voxel can therefore be expressed mathematically as a diffusion ellipsoid or tensor. The long axis of adjacent tensors can be ‘tracked’ to progressively reconstruct the 3D orientation of nerve fibres that represent white matter connectivity. The translation of the tensors into neural trajectories can be achieved through various algorithms, which can be broadly classified as deterministic and probabilistic.

Figure 4-3 Principles of diffusion MRI and tractography (Yamada et al., 2009)
A- Diffusion ellipsoids (tensors). When there is no directionality, the fractional anisotropy (FA) is zero (spherical). A typical tensor of a white matter tract will be cigar shaped. When there are crossing fibres the ellipsoid becomes flattened, resulting in ‘pancake’ tensors (Yamada et al., 2009).

B- Tracking starts at a pixel, and continues along the ellipsoids as long as the adjacent vectors are strongly aligned

C- Axial image of colour fractional anisotropic map, showing posterior corpus callosum.

The most common approach used clinically is deterministic line propagation or streamline techniques, whereby neural connections are mapped by designating at least 2 arbitrary regions of interest in 3D space. Tracking is terminated when a pixel with low fractional anisotropy or a predetermined trajectory curvature between 2 contiguous vectors is reached. These are called stop criteria. The advantage of this technique is that the processing is fairly simple and rapid.

There are 2 main disadvantages to the deterministic method. Firstly, it is inadequate in processing voxels containing multiple fibre orientations, providing unreliable orientation estimates that delineate pathways that do not exist, and fail to identify tracts that do. Since crossing fibres occur in around 90% of white matter voxels, this issue is very important (Jeurissen et al., 2010).

Secondly, DWI is a low signal-to-noise ratio technique, which can also affect the reliability of the estimated orientations. The provision of a single best-fit orientation, at the expense of other possible orientations, can lead to misleading results.

Probabilistic techniques were developed to deal with the issues of crossing fibres, and low signal-to-noise ratios. Many of these techniques are adaptations of simple streamline approaches, but include estimates of fibre orientation uncertainty. These offer more robust tractography, and are increasingly used in modern clinical practice (Farquharson et al., 2013, Tournier et al., 2012b).

The probabilistic approach has two main disadvantages. Firstly, it is slower and so cannot be used interactively. Secondly, it may be harder to interpret visually, since the generated tracts
represent a 3D volume of potential connectivities. Anatomical knowledge is required to filter out which fibres are deemed anatomically incorrect.

Both methods of tractography suffer with difficulties with validation. Validation can be achieved by either comparison with known neuroanatomy, or by comparison with intra-operative electrophysiological testing. Although both methods underestimate the fibre tracts, the probabilistic method seems slightly better in this respect (Yamada et al., 2009). Both methods also suffer from poor interuser reproducibility, with small differences in the regions of interest selected leading to considerable variation in the white matter tracts generated.

Tractography has been applied clinically to the surgical treatment of brain tumours. The corticospinal pathway is the most commonly generated tract, for the treatment of tumours that lie close to the motor cortex. There is now good experience in the use of this tractography, exported onto neuronavigation systems, to aid the decision making process during tumour resection (Coenen et al., 2001, Farquharson et al., 2013)

The optic radiation has also been generated, and this is of particular use in temporal lobe epilepsy surgery. Tractography has demonstrated the considerable variability in the anterior extent of the Meyers loops, ranging from 24mm to 43mm from the temporal pole in one study (Yogarajah et al., 2009). There is some evidence that post-operative visual field defects can be avoided if the surgeon has the optic radiation tractography displayed during surgery. This has been demonstrated in the interventional MRI (iMRI) suite, where intra-operative imaging is used to generate transformation parameters which are then applied to pre-operative tractography to correct for brain shift (Winston et al., 2012a, Winston et al., 2014). It remains to be seen if these results can be reproduced outside the iMRI suite.

4.3 Intracranial monitoring

Intracranial EEG monitoring (ic-EEG) is indicated in patients with medically intractable focal epilepsy, where non-invasive investigations have failed to find a focus (Blount et al., 2008).
Ic-EEG remains the gold standard for identifying the region of tissue that must be removed to ameliorate seizure activity. The decision to proceed to ic-EEG, and the precise location and configuration for surgery, arises from a multi-disciplinary case review with all the non-invasive investigations. Subdural grid electrodes are used to capture foci at the cortical surface. Depth electrodes are used to capture deeper foci in the hippocampus, amygdala, insula, cingulate gyrus and areas of cortical dysplasia at the depth of a sulcus. The capture of foci in a three dimensional way is best achieved with stereoelectroencephalography (SEEG).

Subdural grids and depth electrodes are commercially available, and come in a variety of shapes and configurations. Subdural grids are made of thin sheets of silastic, that have platinum electrodes imbedded at 0.5cm or 1cm intervals. Some epilepsy centres manufacture their own grids. The largest widely available grid is an 8x8 configuration with the electrodes 1cm apart. Other common configurations are 4x8, 4x5 and 2x6. Strip electrodes typically employ a single row of electrodes with a variable number of contacts. Depth electrodes are composed of 4-12 platinum recording contacts with 0.5cm or 1 cm spacing.
4.3.1 Placement of subdural grids

The surgical procedure for ic-EEG is straightforward. A large craniotomy is performed under general anaesthetic, with a wide durotomy to provide extensive exposure of the brain convexity. Subdural grids are placed on the brain surface, to capture the focus of seizure origin and to allow mapping of eloquent cortex. Under continuous irrigation, smaller strip electrodes can be gently slid underneath the margins of the bone flap to sample cortex that is not exposed. In this way a generous coverage of the neocortex can be achieved. The neurologist determines the optimum extent of coverage, and the surgeon refines this plan according to safety, feasibility and anatomical considerations. The exiting wires are tunnelled outside the scalp flap, with great care to minimise the risk of CSF leak. The dura is then closed in a watertight fashion, and the craniotomy closed in the normal way.
4.3.2 Placement of depth electrodes

Placement of depth electrodes through the brain parenchyma into deeper structures may be done in conjunction with grid placement at the time of craniotomy. Alternatively, patients can be investigated by depth electrodes alone, without the need for craniotomy. The electrodes can be placed using frame-based stereotactic techniques (Leksell, Brown-Roberts-Wells, Cosman-Roberts-Wells systems) or frameless stereotactic techniques (Medtronic Stealth, BrainLab), either free hand or by custom-designed guidance tools (Centeno et al., 2011, Nowell et al., 2014b). The frame-based techniques, first popularised by Talairach in Paris, require precise imaging of the intracranial arteries and veins. Historically this was achieved with formal cerebral angiography. More recently it is possible to achieve similar results with non-invasive imaging, such as double-dose gadolinium enhanced T1 weighted MR, or CT angiogram.

4.3.3 Implantation strategy

The ic-EEG implantation strategy should be tailored for individual patients, following discussion between the neurophysiologist and the neurosurgeon at the Multi-disciplinary telemetry meeting.

The main advantage of subdural grids is that a wide superficial cortical coverage is achieved. This allows the precise capture of the epileptic discharges at the surface, and also facilitates mapping of cortical function in the post-operative period. The disadvantages are that implantation requires a large craniotomy, with associated risk of infection and haemorrhage. Also, if the seizure onset zone arises from a deep sulcal surface, there is considerable propagation of epileptiform signal prior to detection at the surface of the brain. This can make localisation very difficult.

SEEG is certainly better at localising the seizure onset zone when it lies deep to the surface, and correctly placed electrodes can trace seizure propagation in 3 dimensions. With accurate visualisation of the intracranial vasculature, 12-14 electrodes can be placed safely
in patients with very low rates of haemorrhage. In general the rates of infection are lower than for implantation of subdural grids, when large craniotomies are required, and the procedure is better tolerated by the patients. The main disadvantages of SEEG are that there is limited sampling of the cortex at the surface of the brain, with limited scope for functional mapping.

In summary, patients with seizure onset at the cortical surface, close to eloquent areas, will be more suited to subdural grid implantation, whereas patients with seizure onset at the depths of a sulcus, or inaccessible areas of cortex, are more likely to benefit from SEEG (Podkorytova et al., 2016). However, in practice epilepsy surgery units tend to favour one technique over another, and preferentially accumulate experience in one approach.

4.3.4 Post-operative course

Following surgery a period of inpatient EEG-video telemetry ensues, usually with a cautious withdrawal of anticonvulsants, to capture the clinically important seizure pattern. Direct brain mapping through grid stimulation can also be performed to guide the limits of cortical resection. The resultant grid map of seizure focus and functional cortex is then used as a road map to inform resective surgery.
5 Stereo-electroencephalography (SEEG)

5.1 Introduction

ic-EEG is indicated in patients with medically intractable focal epilepsy, when non-invasive investigations have failed to define the focus, and if the focus is close to eloquent areas. The accurate identification and resection of the epileptogenic zone (EZ) is the most important predictor of seizure freedom in patients who proceed to surgical resections.

Broadly speaking, the two approaches to implementing ic-EEG are with an array of subdural electrodes and an array of intracerebral electrodes. This chapter describes in detail the use of intracerebral electrodes, in a technique also known as stereo electroencephalography (SEEG.)

5.2 Indications

SEEG is a diagnostic procedure, with no therapeutic value in itself. It is therefore most important that SEEG is only considered in patients with a reasonable chance of progressing to potentially curative surgery. This excludes patients with multifocal or bilateral epilepsy. It should also be avoided in children with hemispheric pathology, and stable or progressive motor deficits, who may benefit from hemispherotomy without presurgical invasive investigation.

There are many reasons why initial presurgical evaluation may fail to localise the EZ. These can be divided into relatively homogeneous groups, shown below.

1. No definitive structural MRI lesion, ictal/interictal scalp EEG partially or fully discordant with ictal clinical semiology.

2. Clear focal structural MRI lesion, ictal/interictal scalp EEG and/or ictal clinical semiology suggestive of wider, extralesional involvement in seizure generation.
3. Ictal clinical semiology discordant with ictal scalp EEG.

4. Either MRI lesion, ictal scalp EEG or ictal clinical semiology suggestive of early involvement of highly eloquent areas when their relationships with the EZ have to be established and functional mapping is needed to define the likely prognosis and risk of resection.

5. Large focal, hemispheric, multifocal or bilateral structural lesions with ictal EEG and clinical evidence of more localised ictal onset.

5.3 Grids v depth

Historically ic-EEG has most commonly been implemented in the UK and US by subdural grids and strips. The obvious advantage to this technique is the high spatial resolution and coverage over the surface of the brain, which is particularly suited to accurate mapping of superficial cortical areas. However, this technique is less well suited to mapping deep epileptic foci, which account for over two thirds of the cortical volume, with significant dissemination of the signal prior to detection at the surface. Furthermore, the use of grids requires a large craniotomy, with associated morbidity and infection risk.

Increasingly, SEEG is being considered as an alternative means to implementing ic-EEG (Gonzalez-Martinez et al., 2012). SEEG has the dual advantage of capturing the seizure activity in 3 dimensions, and in deep cortical areas. There is also reduced morbidity as there is no craniotomy performed, and removal of the electrodes does not require a second operation. The major disadvantage with SEEG is that there is less spatial resolution for the purposes of cortical mapping, providing ‘tunnel vision’ of the covered areas. However, this can be overcome if a suitable number of depth electrodes are placed (Munyon et al., 2015).

5.4 History

The first use of intracerebral electrodes to record electrical activity was in the investigation of the role of subcortical areas in the generation of petit mal seizures (Kirikae and Wada,
1951), and in the investigation of the ‘thalamic’ seizures (Williams and Parsons-Smith, 1949). These were simple techniques; placement was freehand with no neuronavigational assistance, and recordings were short-lasting, and unlikely to detect spontaneous ictal activity.

Two landmark events caused a paradigm shift in the implementation of ic-EEG by depth electrodes.

Firstly, the concept of the EZ, proposed by Luders (Rosenow and Luders, 2001) provided a hypothetical target for investigators to aim for. This target was a hypothesis, based on the available anatomo-electro-clinical evidence that non-invasive presurgical evaluation provided. Importantly, the group of the Saint Anne Hospital in Paris, France suggested the EZ was best considered a dynamic process, incorporating spatiotemporal and multidirectional organisation as opposed to a single Cartesian coordinate. Thus the EZ was felt best defined in a similarly 3D arrangement.

Secondly, the development of stereotaxis (Talairach et al., 1962) provided a means to accurately test the hypothesis of the EZ, by precise placement of depth electrodes in three dimensional space. The arrangement of the electrodes was tailored to the localisation hypothesis, incorporating the complex requirements of the definition in space and time of the epileptic discharge. The aim of this arrangement or ‘exploration’ was to verify or reject the localisation hypothesis of the EZ.

Conceptually the technique of SEEG is a more complex and nuanced method to implement ic-EEG. SEEG requires technical skill in the implantation of the depth electrodes, but also requires a more complex and spatially aware interpretation of recordings. Thus advances in surgical technique were coupled to advances in neurophysiological understanding of epileptic activity.
5.5 Technical implementation

5.5.1 Historical

The grandfathers of SEEG were undoubtedly Talairach and Bancaud, who implemented the first comprehensive methodology of SEEG (Talairach et al., 1962). The aim of the technique is to accurately place a number of intracerebral electrodes in cortical structures, in a tailored arrangement or exploration. There are two main considerations for this.

1. Precise sampling of cortical structures

2. Establishment of avascular planes

As previously discussed, early stereotactic methods overcame interindividual variations in cortical anatomy using a proportional reference system. This system was based on the intercommissural line, as defined by contrast ventriculography (Talairach and Tournoux, 1988).

Vascular anatomy was demonstrated by cerebral angiography. Gabor Szikla developed the technique of stereoscopic teleangiography in stereotactic conditions, which allowed the planning of trajectories in avascular planes (Szikla et al., 1977). The basic technique is to perform a cerebral angiogram in two planes, with a small difference in separation angle. Simultaneous viewing of these angiograms allows the viewer to fuse the images, and develop a perception of depth.

Using these two techniques, Talairach was able to deliver accurate electrode placements in avascular trajectories (Talairach and Szikla, 1980).

5.5.2 Modern techniques

The implementation of SEEG has become simpler with the development of modern neuroimaging. However, techniques still vary between units, with differing layers of complexity, as outlined below.
5.5.2.1  *Two step technique*

Cossu described their experience with SEEG in 60 paediatric patients, using a two-step technique under two separate general anaesthetics (Cossu et al., 2006). This technique uses stereotactic teleangiography coupled to structural MRI. Planning is performed between operations.

In the first step a Talairach frame is positioned on the patient’s head under general anaesthetic, and stereoscopic teleangiograms are obtained in the stereotactic frame. Previously acquired MRI (spoiled gradient echo T1-weighted, gadolinium-enhanced sequence, slice thickness 1mm) are then coregistered to the angiography and imported into a neuronavigation module. The stereotactic frame is removed and the patient is discharged from hospital.

Planning of electrode trajectories is performed between surgeries, on the ‘stereotactic roadmap’ acquired.

In the second step, the frame is repositioned in exactly the same position as in the angiographic study. Electrode placement is implemented using a double grid guide mounted on the frame, and a robotised tool holder to deliver the trajectories. For each electrode a percutaneous trephination of the skull is performed with a 2.3mm twist drill, the dura is perforated by low current monopolar coagulation and a titanium hollow peg is screwed to the skull. A rigid stylet is passed through the peg and advanced to a predetermined depth to trace the intracerebral track of the electrode, and the electrode is then placed under fluoroscopic control.

5.5.2.2  *One step technique*

Gonzalez-Martinez described their adoption of SEEG in a cohort of 100 patients, using a simpler one step technique of implementation (Gonzalez-Martinez et al., 2014). This technique uses digital subtraction CT angiography in preference to stereotactic
teleangiography. Planning is performed prior to patient admission on previously acquired gadolinium-enhanced T1 sequence MRI loaded on a neuronavigation module.

On the day of surgery, the patient is placed in a Leksell stereotactic frame under general anaesthetic, and undergoes a stereo dyna CT and 3D digital subtracted angiogram. The pre-operative MR, stereo dyna CT and angiographic images are digitally processed using a dedicated image fusion software, and the planned trajectories are checked to ensure the absence of traversing vascular structures. Electrode placement is implemented using the Leksell frame, with standard skin incision, skull perforation and dural opening, and placement of a guiding bolt. The electrode is placed under fluoroscopic guidance.

More recently the Cossu group have also switched to a one-step technique, using the O-arm 1000 System, a Medtronic mobile cone-beam CT scanner, to obtain 3D digital subtraction angiography (Cardinale et al., 2013).

Figure 5-1 O arm 3D rotational angiography
In A and B: 2 axial slices are extracted from 2 coregistered datasets without and with contrast medium injection. In C: the result of the algebraic subtraction. D: a
stereoscopic pair of images of 3D volume rendering of the subtracted data set. (Cardinale et al., 2013)

5.5.2.3 Frameless
Frame-based techniques are highly accurate. However, there are a number of disadvantages to these techniques. They are associated with potential patient discomfort, additional time for frame placement, restricted access to the surgical field and a limited ability to define new trajectories in real time during surgery. Frameless stereotactic techniques are more versatile, and offer a further option in SEEG implementation.

Mehta et al describe the implementation of frameless SEEG, using a slotted, custom-designed adaptor built to interface with a commercially available neuronavigation system (StealthStation Guide Frame-DT and 960-525 StealthFighter) (Mehta et al., 2005). In their series of 20 patients, the Cranial Navigation software was used to plan electrode trajectories based on preoperative spoiled gradient echo MRI studies. Electrode delivery was implemented using a Seldinger technique, with a cannula and stylet passed through the custom adaptor and Guide Frame-DT to stop 5mm short of the intended target. Surgical approaches were by either large open craniotomies or burr holes, with clear exposure of overlying cortical vascular anatomy.

5.6 Trajectories
The arrangement of electrodes, or ‘exploration’ should be tailored to each individual patient, to verify or reject the localisation hypothesis of the EZ based on the anatomo-electro-clinical evidence. However, ictal discharges often follow multidirectional trajectories and do not respect the anatomical boundaries of the cerebral lobes (Munari et al., 2000). Thus most explorations are multilobar, incorporating the presumed ictal onset, all the possible structures connected with the ictal onset zone through the common pathways of propagation, and the eloquent regions involved in the discharge. Any exploration should also
include adequate sampling of and around any structural lesion thought to play a role in the epileptic focus.

Cossu et al concede that these principles reject a standardised arrangement of electrodes (Cossu et al., 2005). However, retrospective analysis of previous cases demonstrates a number of typical patterns of coverage.

5.6.1 Temporal lobe
In patients with likely temporal lobe epilepsy, SEEG may be needed to ensure the EZ does not extend to extratemporal areas, or to lateralise the side of the epilepsy. Explorations should target preferential spread of the discharge to the insulo-opercular complex, to the temporo-parieto-occipital junction and to the anterior frontal cortex.

5.6.2 Frontal lobe
Frontal lobe SEEG can often be confined to the frontal lobe to avoid very large sampling areas. This still presents a large sampling area, with several patterns of involvement, including the frontal pole, lateral convexity and mesial frontal area. Placement of rolandic electrodes is not infrequent if there is the suggestion of the involvement of these areas. In the paracentral lobule, intracerebral electrodes are particularly helpful to sample the depth of the rolandic fissure, and the transiting white matter tracts.

5.6.3 Posterior quadrant
SEEG in the posterior quadrant is often multilobular. There is frequent simultaneous involvement of several occipital, parietal and posterior temporal structures, and rapid multidirectional spread to supra- and infra-sylvian regions.
5.7 Insular epilepsy

Insular seizures are usually simple partial seizures, characterised by laryngeal discomfort, dysphonia, paraesthesia and somatomotor symptoms (Kriegel et al., 2012). They can also present in a variety of atypical ways, including cortical gelastic epilepsy (Tran et al., 2014). Insular epilepsy can be difficult to diagnose in the absence of a structural lesion, and often requires ic-EEG evaluation (Nguyen et al., 2009). Further, the concept of temporal plus epilepsy, where seizures appear to be multilobar, involving the temporal lobe as well as neighbouring structures (Kahane et al., 2015), is driving more comprehensive ic-EEG to include the insula and the orbitofrontal cortex. Ic-EEG implementation in the insula is especially suited to SEEG, since the cortical surface is ‘buried’ within the sylvian fissure and not easily amenable to grid placement. There are several approaches to ic-EEG in the insula (Desai et al., 2012).
5.7.1 Craniotomy and direct visualisation

An open approach to the insula involves pterional craniotomy followed by dissection of the Sylvian fissure, retraction of opercular cortex and further dissection across M2 middle cerebral artery branches. Strip electrodes can then be placed over the insula cortex under direct vision. This technique has been described by several groups (Desai et al., 2012). It is most suitable in cases where widespread coverage of temporal and frontal convexities is also required. However, there are obvious disadvantages with this technique, including significant surgical morbidity, and poor ‘contact-to-electrode’ ratios.

5.7.2 Stereotactic orthogonal

This approach was first described by Talairach and Bancaud, and involves the transopercular insertion of multiple axially orientated intracerebral electrodes under stereotactic guidance. This is a well-established technique to sample the medial and lateral insula. The disadvantages are that the trajectories pass through eloquent cortex, and traverse numerous vascular structures. Additionally, the geometry of the insula means that there remains a suboptimal contact-to-electrode ratio.

5.7.3 Stereotactic oblique

Oblique trajectories aim to minimise pial violations, and pass through a safe, non-eloquent corridor of cortex. They avoid the need for craniotomy and cortical retraction, and they also avoid the need to traverse the sylvian fissure. Oblique trajectories may be posterior, entering through the parietal region, or anterior, entering through the frontal lobe. This approach can therefore be tailored to capture relevant extra-insula activity. Both approaches are well suited to the 3D shape of the insula; good ‘contact-to-electrode’ ratios have been reported by different groups, ranging from 5-7 contacts per electrode (Desai et al., 2011). However, both approaches share the disadvantage of poor coverage in the mediolateral axis of the insula. Several groups have taken a combined approach using both the transparietal and transfrontal oblique routes in the same patient (Afif et al., 2008). This has the advantage of...
combining two relatively efficient, low risk methods to enhance coverage, but has the disadvantage of an incrementally increased risk of neurological deficit or vascular injury.

Figure 5-3 Insular SEEG implantations
A- Coronal and sagittal CT-MRI reconstructions demonstrating the posterior oblique trajectory.
B- Coronal and sagittal CT-MRI reconstructions demonstrating the anterior oblique trajectory (Dessai et al., 2011)

5.8 Use of robot

There is great interest in the use of commercially available robot systems to ‘execute planned trajectories’ in targeted surgery. Robot systems are thought to improve the accuracy and dexterity of the surgeon (Cardinale, 2015), with the versatility to reduce tremor or amplify force.

Examples include the Renshaw neuromate stereotactic robot (Li et al., 2002) and the Medtech ROSA robot (Serletis et al., 2014). The use of robot delivery systems in electrode implantation in SEEG is increasingly popular in European and American neurosurgery units. Cardinale et al report their case series of 500 procedures with 6496 implanted electrodes. They describe a shift in practice, from the traditional two-step surgical workflow to a new
simpler workflow, incorporating brain 3D angiography and MRI in frameless conditions, advanced multimodal planning and robot-assisted implantation (Cardinale et al., 2013).

The main barrier to the widespread adoption of robot-assisted surgery is the significant cost of the hardware. Further studies are required to examine whether robot assisted surgery is safer, more accurate and more efficient than traditional frame-based and frameless surgery. Cost/benefit analyses will then be needed to assess the case for widespread adoption.


6 Multimodality Imaging in Epilepsy Surgery

6.1 Principles of multimodality

3D multimodality image integration (3DMMI) refers to the use of a range of different imaging tools that provide distinct, complementary information, to solve a common complex problem. The fundamental concept is that the integration of different data sets onto a single platform confers an added value over the consecutive presentation of the same data sets in series or in parallel.

6.2 Application to Epilepsy Surgery

3DMMI is ideally suited to the planning of epilepsy surgery since it requires the simultaneous analysis of multiple data sets, and the consideration of how each data set relates to another.

3DMMI allows for the optimal evaluation of the spatial concordance of a site of seizure localisation established using different modalities, as well as the relationship of the structural, functional and electrophysiological changes to the anatomical features in the area. It also allows the determination of the proximity of the EZ to eloquent cortex, or the functional deficit zone.

6.3 Co-registration

Image co-registration is the process of transforming images acquired at different time points or with different imaging modalities into the same coordinate system. This can be described in a two-step process:

1. Determination of the 3 dimensional transformation which relates the coordinates of a particular data set to a different data set
2. Application of the transformation to map information from one data set to another.
Since the brain is enclosed within a solid structure (the skull), the transformation can be represented as a linear, spatially invariant function of the form:

\[ x_a = Ax_b + B \]

\( x_a \) is coordinate of point in study A

\( x_b \) is coordinate of point in study B

Matrix A represents rotation and plane reflection

B represents translation

This is known as rigid transformation, and does not incorporate any distortional transformation.

There are 9 transformation parameters in total; three rotation angles, three translation values and three scaling factors. The rotation and translation parameters account for the differences in the orientation and location of the patients head in the different imaging devices. The scaling parameters account for possible mis-calibrations of the imaging devices in the form of scaling.

6.4 Clinical applications

6.4.1 Neuro-oncology

Since the development and wide availability of MRI in neurosurgical practice, 3DMMI has increasingly been used in tumour surgery. High resolution anatomical MRI is sensitive in discriminating healthy from pathological tissue. fMRI is useful in determining the laterality and localisation of a range of somatic and cognitive functions, and DWI can be used to determine underlying white matter connectivity by tractography. Assembling this complementary information onto the same coordinate system is indicated when the tumour is located in or close to eloquent tissue.
The importance of fMRI in therapeutic decision making in neuro-oncology was prospectively evaluated in 2006 (Petrella et al., 2006). Treatment plans changed in 19 out of 39 patients, with 18 patients recommended more aggressive surgical resections. The conclusion was that fMRI enables more aggressive therapeutic approaches in a subset of patients where functional risk is downgraded.

There is increasing evidence that DWI and tractography has useful applications in neuro-oncology, most commonly with lesions close to the motor cortex and corticospinal tract (Bello et al., 2010, Farquharson et al., 2013).

The integration of advanced imaging techniques in the planning of tumour surgery has been aided by the development of commercially available neuronavigation systems, which facilitate a basic model for 3DMMI integration. These systems are limited by the quality of the data sets entered and by flexibility, but represent a real advance in the use of 3DMMI in clinical practice.

6.4.2 Epilepsy Surgery

As stated previously, epilepsy particularly lends itself to 3DMMI. Identification of a structural lesion is a strong predictor for achieving seizure freedom following surgery. Therefore any imaging technique or post-processing tool that can unmask a previously cryptogenic structural abnormality is highly valued.

In paediatric epilepsy the use of FDG-PET, DWI and magnetic source images, has significantly improved lesion detection and localisation, helping identify FCD, tuberous sclerosis, hemimegalencephaly, HS, neoplasms, Rasmussen encephalitis, perinatal infarction and Sturge Weber syndrome (Rastogi et al., 2008).

Similarly, voxel-based morphometric analysis of cortex, comparing individual brain anatomy with a normal database, can identify areas of interest for further investigation (Wellmer et al.,
These regions can then be manual segmented, registered with structural MRI and exported into neuronavigation systems for targeted recordings with depth electrodes.

Figure 6-1 Axial view of MR postprocessing, demonstrating left frontal area of FCD
A: T1WI, B: junction image. C: extension image, D: high resolution Flair (Wellmer et al., 2010)

Several groups have reported on their use of 3DMMI in epilepsy surgery (Murphy et al., 2001, Murphy et al., 2004, Hogan et al., 1999). Murphy reports on a carefully selected cohort of 22 patients, deemed as difficult cases, who underwent 3DMMI guided surgery between April 1999 and October 2001 (Murphy et al., 2004). Criteria for patient selection was no lesion on the conventional MRI, multiple lesions or one very large lesion that could not be safely resected without risk of significant post-operative morbidity. Murphy used PET, FLAIR, SPECT and SISCOM; imaging was coregistered using a Unix-based workstation and commercially available software package (Analyze) and then downloaded onto a neuronavigation system for use in theatre. Murphy also used post-operative CT to incorporate the implanted electrodes into the data set. Murphy notes that the value of functional imaging was the unmasking of previously cryptic regions of interest, and the value of integration was to place this new information in an anatomical and surgically accessible framework. With these added gains, he contended that 3DMMI can improve outcomes in more difficult cases, such as non-lesional extratemporal epilepsy. The seizure outcomes
were recorded as Engel Class I in 17 out of 22 patients, although mean follow up was only 27 months.

3DMMI encompasses not only new functional modalities to unmask new regions of interest, but also modalities to demonstrate vascular anatomy. The incorporation of robust vascular imaging into the anatomic imaging is a pre-requisite to the technique of SEEG, described by Bancaud and Talairach (Talairach et al., 1962) and can also be useful as a roadmap to gyral anatomy in craniotomies (Harput et al., 2014). Optimal results are obtained by direct intra-arterial injection of contrast medium, although this carries the attendant risks of cerebral angiography (Cardinale et al., 2015).

6.5 Current practice

Computerised pre-operative 3DMMI planning currently takes place in three different ways.

1. Basic planning on commercially available neuronavigation systems (Medtronic Stealth Cranial, BrainLab)
2. Specialised planning software as adjunct to neuronavigation software (StealthViz, iPlan)
3. Stand-alone specialised planning software packages (BioImageSuite, Yale University; 3D Slicer; Harvard; Analyze, Mayo Clinic).

6.5.1 Neuronavigation

The most widely used frameless neuronavigation systems in use in Europe and North America are the Medtronic Stealth and BrainLab Navigation systems. Both systems allow import of dedicated navigation data sets from MRI and CT, followed by automated coregistration. Thus it is possible to merge T1 and T2 weighed MRI with CT. There is a basic functionality for building simple 3D model sets according to thresholding, but there is very limited functionality with regards to data processing and analysis, visualisation and presentation.
6.5.2 Specialised planning software as adjunct to neuronavigation software

StealthViz (Medtronic) is a planning software package that is compatible with cranial Stealth Navigation (Medtronic). It is a tool specifically designed for use by neurosurgeons, neuroradiologists and neuroscientists to generate clinically useful 3DMMI and to plan surgery. StealthViz received FDA approval in 2008, and is used in the planning and treatment of a variety of neurosurgical conditions.

There is far greater functionality with regards to data processing, visualisation and presentation. This includes the following:

- Imports scans in DICOM format, including MRI, MR angiography, CTA, fMRI, PET and MEG.
- Visualises data in 2D and seen in fast 3D volume renderings.
- Multiple data sets can be co-registered and fused using the StealthMerge software.
- Manual and semi-automated segmentation of anatomical structures in 2D
- 3D volume renderings
- Generation of fMRI activation maps for display as 3D objects.
- Additional Stealth Diffusion Tensor Imaging software module that builds on the StealthViz engine, enabling rapid tractography of white matter tracks to be generated from DWI. The user can tailor their own tractography using individual regions of interest, although the tractography is deterministic and therefore limited in accuracy.
- Surgical planning and saving for export.
- Export to either picture archiving and communication systems (PACS) or a StealthStation for use in the operating theatre.

6.5.3 Stand-alone specialised planning software packages

The most versatile systems are the stand-alone specialised planning software packages that are developed outside of industry. Examples include BioImageSuite, developed at Yale University, 3D Slicer developed at Harvard and Analyze developed at the Mayo Clinic.
These are used in a range of disciplines in basic and clinical science. The major advantage of these packages is that they are not dedicated to solving specific well-defined problems. This ‘non-specialisation’ means that there is added flexibility in the processing, manipulation and display of data sets, and an added range of tools to choose from.

The practice at the National Hospital for Neurology and Neurosurgery (NHNN) has used the AMIRA software package to facilitate 3DMMI planning and surgery. AMIRA was selected on account of functionality and usability. Using this software our group have demonstrated that multimodality integration is feasible as standard clinical practice in a busy epilepsy surgery centre with a pipeline for intraoperative use by neurosurgeons (Rodionov et al., 2013).

6.6 Amira software

6.6.1 History

AMIRA is an extendable software system for the scientific visualisation, data analysis and presentation of 3D and 4D data. It is developed and commercially distributed by Visage Imaging GmbH, Berlin in cooperation with the Zuse Institute Berlin (ZIB). There is considerable overlap between the development of AMIRA and StealthViz, since they share the same lineage from Visage Imaging GmbH.

AMIRA started development as a research tool in the Department for Scientific Visualisation at the ZIB in 1994, to solve computationally and scientifically challenging tasks in medicine, biology and engineering. The emphasis of the research was to generate a product that was interactive, flexible and intuitive to use for non-computer scientists. The early model was named HyperPlan, in reference to the initial target application of planning hyperthermia cancer treatment.

The versatility and potential applications of HyperPlan led to a rapid uptake by users in a variety of fields. This was associated with an increasing demand for software distribution and support, which exceeded the capabilities of the ZIB. In view of these increasing demands,
HyperPlan was redesigned and relaunched as a commercial supported product in 1999, under the new name AMIRA. Versions of AMIRA are available on the SGI IRIX, Hewlett-Packard Unix, Linux, Microsoft Windows and Mac OS X. The versatile functionality is the key to the success of AMIRA. This versatility can be demonstrated by the range of options and editors available, as well as the endpoint task applications.

Figure 6-2 Examples of AMIRA software advanced visualisation
A- Honeybee Brain visualisation, B- 3D reconstruction from CT knee. C- Microtubule tracing 
(http://www.fei.com/software/amira-3d-for-life-sciences/)
6.7 Barriers to widespread adoption

There are three barriers to the widespread adoption of 3DMMI in clinical practice:

1. Organisational infrastructure
2. Accuracy
3. Validity.

6.7.1 Organisational infrastructure

3DMMI is a complex addition to any clinical pathway, which requires considerable changes in organisational infrastructure. The first requirement is the availability of the range of imaging modalities, along with the time and expertise to perform relevant pre-processing of data. The second requirement is a dedicated service of data integration and validation, which requires specialist training and can be costly in terms of man hours. We estimate that a complete data set for a patient requires 8-12 hours work with the use of at least 4 GB of random access memory (RAM). The third requirement is a common consensus by the entire multi-disciplinary team to engage with the program, accepting that adoption is accompanied by a learning curve in how best to present and use the data. There are significant start-up and running costs with 3D multimodality integration, and to date there is no evidence that this is a cost-effective tool in clinical practice.

6.7.2 Accuracy

The old adage by Aristotle, ‘You get out what you put in’ is especially pertinent to 3DMMI as some data sets will be reliable and reproducible such as structural MRI, and other sets will have considerable inter-user variability such as tractography (Heiervang et al., 2006). Some data sets are further limited by their own biophysical principles; for example, blood oxygen level dependent signal in fMRI is an indirect measure of neuronal activity, and tractography is a presumption of white matter connectivity. Interpretation of these within an integrated data set requires differential levels of caution and confidence.
Integration and presentation of multimodal imaging is a step-wise process of spatial co-registration, and each step carries a margin of error. For this reason it is essential that co-registration is checked manually, and that errors in anatomical localisation such as laterality, are checked at each stage. We aim for a coregistration accuracy of 3mm in plane, which is similar to the spatial resolution of fMRI, tractography, PET and SPECT.

For 3DMMI to be available to the neurosurgeon in theatre, the data sets are exported to a neuronavigation system, and a further registration takes place between the 3D model and the patient’s head. This adds a further margin of error, which is dictated by the neuronavigation software and quality of registration.

The accuracy of this spatial registration further deteriorates as the surgical procedure takes place, due to brain shift. This is the intraoperative displacement and distortion of the brain that inevitably occurs during operations, as a result of CSF loss, gravity, brain swelling and brain resection.

The aggregation of these margins of error has to be considered as the neurologist or neurosurgeon integrates this additional tool into clinical practice.

6.7.3 Validity

A further barrier to the widespread use of 3DMMI is the absence of evidence, to the present time, that this is a clinically useful tool. In our experience the tool has been helpful in the planning and performing of surgery, although we acknowledge the possibility of observer bias. This method does not lend itself easily to randomised controlled trials, and alternative evaluations such as comparison with historical cases, and studies of the effect of disclosure of 3DMMI data on decision making are necessary (see chapter 11).
7 Advances in Epilepsy Surgery*

7.1 Introduction

Despite advances in imaging and the accumulation of neurological and surgical experience, the outcomes for seizure freedom in epilepsy surgery have not changed significantly over the last 20 years. Currently 20-40% of patients with epilepsy are considered refractory to medical treatment (Tellez-Zenteno et al., 2005). Less than 50% of these are candidates for focal resective surgery, with rates of long term seizure freedom ranging from 30-60% depending on the operation (De Tisi et al., 2011). Some argue that this apparent lack of progress is a reflection of a lowered threshold to offer surgery, and that with continued refinement of techniques increasingly challenging cases are being taken on. However, there is widespread agreement that there remains great potential to improve non-pharmacological management, to achieve either better seizure control or complete seizure freedom.

There are three broad directions in which the next major advances may occur. Firstly, there is the continued refinement of the current methodology. An improved hypothesis for the EZ, based on advanced presurgical evaluation including ic-EEG, and thus better patient selection for cortical resections. This is probably most relevant to sufferers of nonlesional extratemporal epilepsy, and is most likely to lead to improvements in the rates of seizure freedom. Next, there are improved surgical methods for achieving a precisely targeted cortical or subcortical resection. These can be grouped as neuroablative techniques, and include disconnection of propagation pathways, and destruction of epileptogenic foci. Neuroablation may be applied in the treatment of both focal and generalised epilepsy. Thirdly neuromodulation may take a broader role, with the possibility to improve quality of life and be a useful palliation. This is most applicable to patients who are currently not candidates for resective epilepsy surgery, because their epilepsy arises from eloquent cortex, is multifocal or generalised. Neuromodulation will not be discussed in this chapter, but has been reviewed elsewhere (Nowell et al., 2014a).

7.2 Refinement of current methodology

7.2.1 The epileptogenic index

The purpose of presurgical evaluation is to define the EZ, and to define the surrounding functional deficit zones. The notion of a single discrete area of EZ is attractive in its simplicity, although the high failure rate of resective surgery runs counter to this. Rather it is possible that in at least some cases there are several structures involved in epileptogenesis, and a more comprehensive notion of the EZ needs to be considered.

The characteristic electrophysiological pattern of the EZ is the presence of high-frequency oscillations or ‘rapid discharges’. There is much interest in using the spatial distribution of high frequency oscillations as a potential marker to guide decision making and cortical resections (Holler et al., 2015), although further work is needed to elucidate the efficacy of this approach (Gloss et al., 2014).

Bartolomei in 2008 introduced the concept of the ‘epileptogenic index (EI)’, a novel quantitative measure that characterises the epileptogenicity of brain structures recorded with depth electrodes (Bartolomei et al., 2008). The EI is based on both spectral and temporal factors, with statistically high values corresponding to structures involved early in the ictal process. They found that their measure of EI effectively distinguished between mesial temporal lobe epilepsy and lateral neocortical epilepsy. Furthermore, in mesial temporal lobe epilepsy (MTLE) they found a statistically significant correlation between the duration of epilepsy and the number of structures disclosing high EI values, suggesting that MTLE is a gradually evolving process which progresses over time.

Visualisation of the EI, in 3D space as part of an integrated multimodal model, is the obvious next step. This would provide an alternative to the ESI, but also provide a more detailed, contoured brain map of seizure likelihood, that could be used by the surgeon to stratify the risk-benefit ratio of cortical resection. Work is already underway to make this a reality. David
et al in Grenoble report the use of statistical parametric mapping to visualise a quantification of the seizure onset zone (David et al., 2011). This has been applied to case studies of insular epilepsy, and also group studies on MTLE. This technique offers much promise in future research and clinical practice.

7.2.2 Advances in imaging

The rates of seizure freedom following resective surgery in sufferers of nonlesional extratemporal epilepsy remain poor (De Tisi et al., 2011). It is clear that better patient selection is required in these cases, with improved methods for imaging the EZ and guiding the implantation of ic-EEG. For some time there has been interest in unmasking previously occult structural lesions, using non routine MRI sequences and voxel-based morphometric analyses (Focke et al., 2009). There are also developmental techniques such as EEG-fMRI which require refinement and further evaluation in clinical practice (Zijlmans et al., 2007).

Increased use of 3DMMI is also likely to be important. The feasibility of this additional tool in a busy epilepsy surgery practice has already been demonstrated (Rodionov et al., 2013) and chapter 10 describes a prospective study to validate the usefulness of this in presurgical evaluation and surgical management. Ultimately improvements in the surgical outcomes in this patient group will depend on better imaging, including visualization of electrical abnormalities in 3D, reliable imaging integration and robust planning and implementation of ic-EEG (Fig 7-1).
7.3 Neuroablation

There is an increasing trend in all forms of surgery towards minimally invasive techniques. This is most pertinent for neurosurgery, which often requires access to deep parts of the brain. Accurate navigation to these areas without the need for significant brain retraction has been solved by the application of stereotaxis. However, there remains the problem of how to ‘execute’ the surgery once instruments have been safely navigated to their targets. This problem is best framed in the context of epilepsy surgery with cortical resection following SEEG. However it is also possible to consider patients with HS, where even ‘selective’ amygdalohippocampectomies carry the risk of new cognitive deficit.

There are a number of interesting alternatives to ‘execute’ lesioning at the site of the EZ or to cause a disconnection in a minimally invasive way.

7.3.1 Radiofrequency (RF) thermocoagulation

There is much interest in complementing the technique of SEEG with a therapeutic component to lesion cortex that is sampled by the electrodes. The most obvious solution is
by thermocoagulation, using a RF generator connected to the electrode contacts. A feasibility study from Lyons described this technique in 2004 in 20 patients undergoing SEEG implantation (Guenot et al., 2004).

There are several benefits with this technique. It builds on the SEEG method that is well-established, and proven to be safe and reliable. It is well tolerated by the patient and does not require general anaesthesia. Multiple sites can be lesioned, with real time clinical and electrophysiological feedback. Finally, this method does not preclude the possibility of subsequent conventional open surgery.

One disadvantage with this technique is that there is no real time feedback on the lesioning process with regards to local temperatures. The operator relies on an abrupt decrease in current to indicate coagulation of surrounding cortex. Also, RF thermocoagulation is known to be an inherently imprecise mode of thermal energy delivery, with theoretical risk to surrounding structures.

Overall the results for SEEG and RF thermocoagulation are modest. A case series of 41 patients from the Lyons group report that 20 (48.7%) experienced a significant decrease in seizures of at least 50%, and 21 (51.3%) did not benefit from the procedure (Guenot et al., 2011). More recently a study of 89 patients showed persistent improvement in seizure control in 25 (28.1%) (Cossu et al., 2015). This technique has also been applied to MLTE, where more extensive ablations were seen to be better than limited ablations, although neither were equivalent to the standard ATLR (Parrent and Blume, 1999). These results suggest that RF thermocoagulation may be a low risk, palliative procedure, which can be considered as first line treatment in patients undergoing SEEG to improve seizure control. It seems that this technique is particularly suited to patients for whom conventional surgery is contra-indicated or considered too high risk, such as patients with deep epileptogenic heterotopic nodules (Cossu et al., 2015).
7.3.2 MR-guided focused Ultrasound

Magnetic resonance-guided focused ultrasound surgery (MRgFUS) is an accurate method of delivering high doses of transcranial ultrasound energy to a discrete intracranial focal point (Monteith et al., 2013). The major historical barrier to this method was the need to create a craniectomy window prior to treatment, to prevent the ‘defocusing’ effect of the skull. However, recent advances in phased array transducer technology have overcome this defocusing effect, so that the treatment can be administered in a ‘closed’ method without the need for conventional surgery.

The MRgFUS consists of a clinical 3 Tesla MRI, with a transcranial hemispheric array transducer that has 1024 ultrasound elements. The patients head is fixed to the system in a stereotactic frame and the transducer is filled with degassed water to allow ultrasound waves to propagate toward the patient’s head. Treatment planning is based on MRI, and magnetic resonance thermometry is used for target verification during the procedure. The treatment can be administered on an outpatient basis, and treatment effect can be monitored by post operative MRI (Figure 7-2).
MRgFUS has previously been used to execute a selective medial thalamotomy in the treatment of chronic neuropathic pain (Martin et al., 2009). An FDA-approved phase I trial using MRgFUS thalamotomy in the treatment of essential tremor has been completed, and showed clinical improvements in 15 patients (Elias et al., 2013). There are plans for further trials in the treatment of metastatic brain tumour and Parkinson’s disease.

MRgFUS has obvious and compelling attractions in epilepsy surgery. There is the avoidance of any latency period or the risk of secondary tumours with ionising radiation, which comes with radiosurgery. There is the convenience of the treatment, which does not involve any skin incision and therefore avoids the surgical risks of infection, haemorrhage and wound dehiscence. There are no trajectory restrictions and crucially there is near real time feedback of the lesioning effect, with thermometry.
The main concern with MRgFUS is the risk of inadvertent heating of the skull base and critical structures such as cranial nerves, which results from the ‘shadow’ effect of energy distal to the focal point of the target. Cadaveric studies have yielded techniques to minimise this collateral heating, by building into the system software certain ‘no pass’ areas at the base of the brain (Monteilh et al., 2013). However, this remains a significant barrier at present to the use of MRgFUS to lesion cortical and subcortical targets. In theory MRgFUS should evolve to become an important treatment modality in epilepsy surgery, although it is important to note there are no current cadaveric or clinical trials underway to determine efficacy.

7.3.3 Laser ablation

Ablation can also be achieved by MRI-guided laser interstitial thermal therapy (MRgLITT). The commercially available Visualase Thermal Therapy System (Medtronic) combines a 15W 980nm diode laser and cooled laser application system with an image-processing workstation. The applicator is inserted to reach the target by a stereotactic method, and laser treatment is applied in the MR scanner, with thermal imaging to visualise the thermal ablation.

MRgLITT avoids the complications associated with radiosurgery. The ablation is more precise than that achieved with RF thermocoagulation, and has reliable real time feedback. Furthermore it appears to avoid the heating of the skull base seen in ultrasound ablation. MRgLITT is a stereotactic surgical procedure, however, and therefore carries the surgical risks of haemorrhage and infection.

This technology has recently received FDA clearance for ablation in neurosurgery, and has previously been reported in the treatment of brain metastases (Carpentier et al., 2008). A recent study describes the initial use of this technique in the treatment of focal epilepsy in 5 children (Curry et al., 2012). Lesions included a cingulate tuber, HS, hypothalamic hamartoma (HH) and FCD. There were no complications, and early experience indicates
that this is a safe procedure. All patients were seizure free at the time of print, but follow up is short and no meaningful information can be drawn on long term efficacy at present. A pilot study is currently underway, which will examine longer term seizure outcomes in 20 patients. It is our view that MRgLITT is an exciting prospect, which is closer to clinical adoption in epilepsy surgery than is MRgUS.

7.3.4 Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a well-established technique that uses focused ionising radiation to target deep-seated lesions, sparing damage to surrounding tissue. The ionising radiation breaks chemical bonds and results in the production of free radicals. Ionising radiation can be generated by proton beam accelerators and photon accelerators. The most widely used sources of ionising radiation are linear accelerators (LINAC) and photon accelerators such as Cyberknife and Gamma Knife.

The main advantage of SRS is that deep seated and multiple lesions can be treated with no surgical approach, avoiding the inherent brain retraction/injury. The main disadvantages include the latent period of efficacy, collateral tissue injury secondary to radiation, and late onset secondary malignancies. Furthermore, the efficacy of SRS in the treatment of different conditions is not fully understood.

The anticonvulsant effects of SRS were first observed in the treatment of tumours and vascular lesions (Quigg et al., 2012). SRS has also been used as a disconnection technique in the treatment of generalised epilepsy by corpus callosotomy (Bodaghabadi et al., 2011). Current interest is centred mainly on the treatment of HH and HS.

7.3.4.1 Hypothalamic hamartoma (HH)

SRS is increasingly being considered for the treatment of HH. Treatment is best done in early childhood, before the development of secondary generalised seizures, behavioural
problems and developmental delay. In selected cases, conventional open surgery offers higher rates of seizure freedom, with the pooled results from multiple studies showing seizure freedom rates from open surgery at 50% and SRS at 30-40% (Frazier et al., 2009, Regis et al., 2000, Pati et al., 2013). However, depending on the characteristics and location of the HH, open surgery may be considered too hazardous and SRS is the obvious alternative (Rosenfeld and Feiz-Erfan, 2007) SRS can also be used in conjunction with open surgery in patients with large HH, if surgical debulking leaves an unresectable residual epileptogenic intrahypothalamic component (Romanelli et al., 2012).

7.3.4.2 Hippocampal sclerosis (HS)
The use of SRS in the treatment of HS is controversial, since conventional anterior temporal lobe resections offer a proven and reliable treatment method. The theoretical advantage of SRS is that the EZ may be lesioned in a selective way, without injury to the lateral neocortex and corresponding neuropsychological complications.

The results of an early prospective multicentre trial on the efficacy of SRS in the treatment of MTLE were promising, with seizure outcome at 2 years comparable to that of standard surgery (Regis et al., 2004). No significant cognitive deficits were seen, and in fact 20% experienced some degree of cognitive improvement. This compares favourably to standard surgery in which cognitive impairment, particularly memory and word-finding, is observed in 30% and improvements are seen in 10-20% (Baxendale et al., 2008).

A further multicentre prospective trial in the US randomised patients to SRS with high (24 Gy) or low (20 Gy) dose delivered to the targets (Barbaro et al., 2009). At 3 years, seizure freedom was 77% in the high dose and 59% in the low dose group. Again, the neuropsychological profiles compared favourably with results from conventional surgery.

Despite these results, there remain questions on the use of SRS in MTLE. There are a number of published series that do not give the same efficacy rates in terms of seizure outcome (Hoggard et al., 2008, Vojtech et al., 2009) Interpretation of these is complicated by
differences in protocol, including dose, isodose centres or ‘shots’, and volume, but the discordance in results should not be ignored.

The rate of optic radiation injury appears to be similar to that seen in conventional open surgery, with homonymous field defects seen in 43-50% (Regis et al., 2004, Barbaro et al., 2009). This is a significant risk in those patients who become seizure free and aspire to gain a driving license, and compares poorly with the results of open surgery in which intra-operative visualisation of optic radiation tractography is employed (Winston et al., 2014).

Finally there are unique risks with SRS that are not seen with conventional surgery, which may be related to the latent time course. Progressive radiological changes are observed, with the development of dose dependent T2 hyperintensity, contrast enhancement and vasogenic oedema with mass effect at 9 months post operatively and peaking at 12 months. These changes correspond to declines in complex partial seizures and transient increases in auras. 70% of patients in the Barbaro study also report new onset headaches post-operatively, although the timing of these is not predictable (Barbaro et al., 2009).

A National Institutes of Health funded multicentre randomised controlled trial, the Radiosurgery or Open Surgery for Epilepsy (ROSE) trial, was designed to answer these outstanding questions. The trial randomised patients with MTLE to conventional surgery or SRS, and was to compare seizure outcome, cognitive outcome, QOL and cost with an initial 3 year follow up. Unfortunately recruitment to this trial has currently stopped, with poor recruitment cited as the reason, and the continued funding of the work is in doubt. Without class 1 evidence, the relative merits of these two treatment paradigms will likely remain unclear.

7.3.4.3 Extratemporal epilepsies
There are no reports on the use of SRS in nonlesional extratemporal epilepsy. Certainly the prerequisite need for ic-EEG to determine the EZ would negate the main benefit of SRS as a non-invasive procedure. However, since other ablative methods have their own
disadvantages, and so far produce only modest results, SRS should not be completely dismissed as a possibility.

7.4 Summary

There are several exciting avenues for further technological advances in the surgical treatment of epilepsy surgery.

For patients undergoing open surgery, improving their outcomes will depend on the stepwise refinement of current methodology, with advances in imaging epilepsy paramount. For patients who are currently not candidates for open surgery, increased delivery of treatment options by minimally invasive techniques, either neuromodulatory or ablative in nature is likely to occur in the future.

There is no consensus on the most promising technique for neuroablation, and competition between different methods will continue. In terms of clinical implementation there are already centres that use SRS and SEEG-guided RF routinely, whilst MRgLITT is undergoing early clinical trials and MRgFUS remains very much a research tool in epilepsy. One major disadvantage of neuroablation in general is that the size of the lesioning is limited, and large, effective ‘resections’ can only be achieved by the repeated lesioning of different contiguous targets. For SEEG guided RF and MRgLITT, this entails repeated passage of hardware through the brain, with associated risk of vascular injury. The precise targeting of individual propagation pathways and epileptogenic foci is therefore likely to be a largely palliative measure, with the eventual emergence of previously masked pathways and foci to continue seizure propagation following surgery. Unfortunately this may be an unsurmountable limitation with neuroablation when compared with conventional open surgery and cortical resection.

Unfortunately epilepsy surgery remains a significantly underutilised resource. It is often perceived as a treatment of last resort, with patients typically referred after 20 years of seizures (Engel et al., 2012). This contrasts with the NICE guidelines, which recommend
referral to a tertiary service if epilepsy is not controlled within 2 years (NICE clinical guideline 137, 2012). This also runs counter to the evidence that epilepsy surgery is a cost effective treatment, with large savings in seizure-free patients as anti-convulsants and hospital admissions are successfully eliminated (Langfitt et al., 2007). Perhaps the most important advance for the future would be to increase awareness in the general population, and education amongst health professionals, on the safety and efficacy of epilepsy surgery as an early intervention in medically refractory focal epilepsy.

Early referrals to tertiary centres, coupled with the rigorous application of systematic presurgical evaluation pathways in a multi-disciplinary environment and with 3DMMI, may be the simplest and surest way to advance epilepsy surgery in the near future.
8 Summary

8.1 Broad Aims

The broad aim of this thesis is to examine ways in which the presurgical evaluation and surgical planning for epilepsy can be optimised and simplified with novel imaging techniques and translational methods. For this work an adult patient population is used, although many of the techniques described can be applied to the paediatric population.

Optimisation and simplification can be achieved by creating a platform for 3DMMI, visualisation and planning, that supports decision-making throughout the patient journey and that can be used in a busy clinical practice. Work described in this thesis has run parallel with and is supported by the development of EpiNav™, dedicated software for use in Epilepsy Surgery. EpiNav™ has been used in the studies listed in chapters 11-14, and has proved crucial in clinical practice in image integration and visualisation, and the planning of SEEG cases.

At the same time our group has explored other ways to simplify the practise of epilepsy surgery in a way that optimises care and that is reproducible in other centres. This includes the development of a frameless method for implementation of SEEG.

In summary, this thesis aims to provide a coherent package of measures that can optimise the practice of epilepsy surgery and that can be easily translated to other centres at little extra cost. A more detailed summary of specific aims is outlined below in the overview of chapters 10-14.

8.2 Overview of chapters (Specific Aims)

In chapter 10 I examine the unmet need for 3DMMI in epilepsy surgery through an online questionnaire that is distributed to centres worldwide. The aims are to determine how frequently these tools are used in clinical practice and to identify the barriers to uptake. This
will inform the development of EpiNav™, software for image integration, 3D visualisation and surgical planning in epilepsy.

In chapter 11 I assess the utility of 3DMMI in the presurgical evaluation of epilepsy. The hypothesis is that the presentation of 3D integrated data sets confers an added value over the presentation of the same data sets in series and changes clinical decision-making. I identify two ‘milestone’ points during presurgical evaluation and assess the impact of 3DMMI at each stage.

In chapter 12 I apply the automated multi-trajectory planner in EpiNav™ to a cohort of 18 historical SEEG cases that were planned conventionally. I test the hypothesis that computer-assisted planning provides implantation plans in real time that are safer and more efficacious, and are feasible in clinical practice.

In chapter 13 I describe a novel technique for implementation of SEEG with a frameless method and I report on the accuracy of this technique in delivering electrodes to their target points. This frameless technique complements the use of EpiNav™ for surgical planning and is broadly aligned with our goals of making the pipeline for Epilepsy surgery simpler for dissemination.

In chapter 14 I describe a study on the relationship between language lateralisation determined with fMRI and tractography to quantify the symmetry of structural connections of language areas. Using constrained spherical deconvolution tractography and EpiNav™ image integration the hypothesis is that Meyer’s loop asymmetry is secondary to asymmetric development of language lateralisation in individuals. For this study I use a historical cohort of patients with temporal lobe epilepsy who have previously undergone advanced imaging investigations.
9 Study design and generic methods

9.1 Introduction

The studies described in this thesis involve a cohort of patients with refractory epilepsy undergoing either presurgical evaluation or surgical treatment. They were prospectively recruited at the NHNN and followed up longitudinally.

This chapter introduces the cohort, the clinical and demographic features and the main assessments undertaken. This chapter also describes the use of the AMIRA software in clinical practice and the development of the EpiNav™ software that was subsequently introduced.

9.2 Subjects and recruitment

9.2.1 Source of patients

Individuals with medically refractory epilepsy undergoing presurgical evaluation for placement of ic-EEG and neocortical resection were invited to participate in the studies detailed in chapters 11, 12 and 13. Patients were identified from the weekly Multi-disciplinary EEG meeting, from direct referrals from Neurology consultants and by consulting the surgical waiting lists. Patients were contacted by telephone or in person at the Epilepsy Society (ES), Chalfont by a Clinical Research Fellow and invited to participate.

9.2.2 Ethical approval

This project was approved by the Joint Research Ethics Committee of the NHNN, and University College London (UCL) Institute of Neurology (ION). All participants were provided with written, informed consent sheets and patient information sheets which are included in the Appendix.
9.2.3 Clinical and demographic characteristics

A total of 96 patients were recruited into the study from August 2012 to June 2015. The outcomes of these patients are illustrated in Table 9-1. The clinical and demographic features of the cohort are shown in Table 9-2.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantation</td>
<td>69</td>
</tr>
<tr>
<td>Resection</td>
<td>35</td>
</tr>
<tr>
<td>Excluded from resection</td>
<td>20</td>
</tr>
<tr>
<td>Awaiting resection</td>
<td>4</td>
</tr>
<tr>
<td>Undecided</td>
<td>6</td>
</tr>
<tr>
<td>Declined resection</td>
<td>2</td>
</tr>
<tr>
<td>Terminated ic-EEG prematurely</td>
<td>2</td>
</tr>
<tr>
<td>Awaiting ic-EEG</td>
<td>7</td>
</tr>
<tr>
<td>Declined ic-EEG</td>
<td>3</td>
</tr>
<tr>
<td>Direct resection</td>
<td>5</td>
</tr>
<tr>
<td>Direct resection</td>
<td>4</td>
</tr>
<tr>
<td>Awaiting direct resection</td>
<td>1</td>
</tr>
<tr>
<td>Medical management</td>
<td>9</td>
</tr>
<tr>
<td>Awaiting Epilepsy Surgery Telemetry Meeting</td>
<td>1</td>
</tr>
<tr>
<td>Undecided</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>96</td>
</tr>
</tbody>
</table>

Table 9-1 Outcomes of the Implantation Cohort
### Table 9-2 Clinical and demographic details of the Implantation cohort

(age and duration given as ranges with median in brackets, ILAE outcome given at end of study period excluding patients with less than 1 year follow up)

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Number</th>
<th>Age (yrs)</th>
<th>Duration (yrs)</th>
<th>M/F</th>
<th>Implantation</th>
<th>Resection</th>
<th>ILAE 1 outcome</th>
</tr>
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<tbody>
<tr>
<td>Temporal</td>
<td>29</td>
<td>21-60 (34)</td>
<td>4-41 (18)</td>
<td>15/14</td>
<td>22</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>FCD</td>
<td>5</td>
<td>21-46 (31)</td>
<td>7-29 (14)</td>
<td>4/1</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HS</td>
<td>2</td>
<td>32-48</td>
<td>40</td>
<td>2/0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lesional</td>
<td>12</td>
<td>31-60 (45)</td>
<td>4-41 (20)</td>
<td>6/6</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Dual lesion</td>
<td>1</td>
<td>47</td>
<td>30</td>
<td>0/1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nonlesional</td>
<td>9</td>
<td>28-57 (33)</td>
<td>10-30 (19)</td>
<td>3/6</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Extratemporal</td>
<td>67</td>
<td>19-62 (35)</td>
<td>4-46 (19)</td>
<td>45/19</td>
<td>47</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>FCD</td>
<td>23</td>
<td>21-62 (35)</td>
<td>5-46 (24)</td>
<td>15/8</td>
<td>15</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Lesional</td>
<td>12</td>
<td>19-54 (39)</td>
<td>4-35 (21)</td>
<td>7/5</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Encephalomalacia</td>
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<td>22-44 (33)</td>
<td>5-31 (11)</td>
<td>6/3</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Nonlesional</td>
<td>23</td>
<td>20-54 (32)</td>
<td>4-45 (16)</td>
<td>20/3</td>
<td>19</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

9.3 Study protocol

9.3.1 Clinical assessment and image acquisition

All patients had complete presurgical evaluation for epilepsy surgery, comprising of structural MRI scans performed at 3 Tesla, video EEG telemetry, neuropsychology and neuropsychiatry. Some patients had additional investigations including FDG-PET, ictal SPECT, EEG-fMRI, MEG, DWI and fMRI as part of standard clinical practice. Patients undergoing intracranial implantation also had dedicated vascular imaging, comprising of 3D
phase contrast MRI to identify cortical veins, and CT angiography to identify intracerebral arteries. The specifications of the various imaging techniques is shown in Table 9-3.

The pre-processing of DWI data and vascular imaging was completed by this group and is described in detail below. Pre-processing of fMRI, MEG, ictal-interictal SPECT and FDG-PET was all done by third parties, independent of this group, and was incorporated in either dicom or nifty format. It is important to note that pre-processing is an important component to this work, but is site-specific and dependent on a unit’s experience and expertise, and availability of modalities. Our group acknowledge that this is a potential limiting factor in the translation of our methods to other units.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Site</th>
<th>Scanner</th>
<th>Pre-processing</th>
<th>Field of view (APxRLxIS)</th>
<th>Voxel size (APxRLxIS)</th>
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</thead>
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<td>3D T1 FSPGR</td>
<td>ES</td>
<td>GE 3T Signa HDx*</td>
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<td>256x256x166</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>GE 3T MR750**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronal T2 FLAIR</td>
<td>ES</td>
<td>GE 3T Signa HDx*</td>
<td>No</td>
<td>256x160x32</td>
<td>0.94x1.5x3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GE 3T MR750**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Navigation T1 with gadolinium</td>
<td>NHNN</td>
<td>Siemens Avanto 1.5T</td>
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<tr>
<td>MRI 3D phase contrast</td>
<td>NHNN</td>
<td>Siemens Avanto 1.5T</td>
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</tr>
<tr>
<td>Imaging Modality</td>
<td>Institution</td>
<td>Equipment Details</td>
<td>Used</td>
<td>Resolution</td>
<td>Slice Thickness</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------</td>
<td>------------------------------------</td>
<td>------</td>
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</tr>
<tr>
<td>CT angiogram</td>
<td>NHNN</td>
<td>Siemens Somatom Definition AS</td>
<td>No</td>
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<tr>
<td>MEG dipole</td>
<td>NHNN</td>
<td>VSM Medtech</td>
<td>Yes</td>
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<tr>
<td>Ictal-interictal SPECT</td>
<td>UCLH</td>
<td>GE Discovery 670</td>
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<td>128x128x49</td>
<td>3.9x3.9x3.9</td>
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<tr>
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<td>UCLH</td>
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<tr>
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<td>128x128x60</td>
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<td>Functional MRI</td>
<td>ES</td>
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<td>128x128x58</td>
<td>1.87x1.87x2.5</td>
</tr>
</tbody>
</table>

Table 9.3 Imaging Modalities used in this series
*up to December 2013, **from December 2013

(ES-Epilepsy Society, NHNN-National Hospital for Neurology and Neurosurgery, UCLH- University College London Hospital, FSPGR-FastSpoiledGradientRecalledEcho, MEG-magnetoencephalography, SPECT-single photon emission computed tomography, FDG PET- fluorodeoxyglucose positron emission tomography, DTI-diffusion tensor imaging, AP- anterior posterior, RL – right left, IS – inferior superior)

9.3.2 Diffusion Weighted Imaging (DWI)

9.3.2.1 Acquisition
Pre-operative MRI studies were performed on a 3T GE Excite II scanner (General Electric, Waukesha, Milwaukee, WI), which was upgraded to a 3T GE MR750 in December 2013. DWI data were acquired using a cardiac-triggered single-shot spin-echo planar imaging sequence with echo time (TE) of 74.7 ms. 60 contiguous axial slices of 2.4mm thickness were obtained covering the whole brain, and diffusion-weighting gradients were applied in 52 non-collinear directions (Cook et al., 2007) with a b-value of 1200 s/mm², along with six non-diffusion weighted scans. The field of view was 24 x 24 cm, and the acquisition matrix size was 96 x 96, acquired with parallel imaging with an acceleration factor of 2. The acquisition matrix was zero-filled to 128x128 to give a reconstructed voxel size of 1.875mm x 1.875mm x 2.4mm. The acquisition time was approximately 25 minutes (depending on subject heart rate).

9.3.2.2 Preprocessing
The scans were transferred to a Linux workstation, and corrected for eddy current correction distortion using the eddy_correct tool in FSL (Smith et al., 2004). DWI data were processed using the MRtrix software package 0.2.12 (http://www.brain.org.au/software/) to produce a fractional FA map, DTI and constrained spherical deconvolution (CSD) fibre orientation distributions (Farquharson et al., 2013, Jeurissen et al., 2010, Tournier et al., 2012a). CSD is a higher order model for estimating fibre orientation, which uses high angular resolution diffusion-weighted imaging (HARDI) to generate estimates within each imaging voxel. We used a maximum harmonic order (Lmax) of 8, and obtained single fibre response functions from all voxels in the brain with FA values of 0.7 or higher. This has been shown to be a robust technique in solving the problem of multiple crossing fibres.

9.3.2.3 Tractography
Regions of interest were generated in native space on the FA map using the MRtrix software package. Tractography was carried out using probabilistic tractography in MRtrix (using the SD_PROB command), using a minimum curvature radius of 1 mm, a step size of 0.2 mm,
and a minimum fibre orientation distribution (FOD) amplitude of 0.1, to generate 1000 tracts from the seed region that met all inclusion and exclusion criteria.

The resulting tracts file were converted into a map of the fraction of tracks to enter each voxel, using the tracks2prob command, and exported in nifty format to EpiNav™. For display purposes, the tracts were thresholded at 5%, representing a compromise between retaining anatomically valid tracts and removing obviously artefactual connections.

9.4 AMIRA software

9.4.1 Image integration on AMIRA

Data integration was performed on a single workstation using the AMIRA (Visualization Sciences Group, Massachusetts, US) software package. This is a stepwise process by which each new modality is co-registered with the base anatomical image, and display settings are adjusted using a range of tools to offer optimal data presentation and visualisation.

9.4.2 Reference image

The base anatomical image is the T1 Stealth MRI post gadolinium. This provides the anatomical information on which all other modalities can be overlaid. Visualisation of this data set in the axial, coronal and sagittal plane is done with the orthoslice tool.

9.4.3 Coregistration

9.4.3.1 Single images

Co-registration is a rigid-body (6-parameter) process, made up of translation and rotation. This is achieved in AMIRA using the manual transform editor function, and then fine-tuned by the automated affine registration tool. The registration is checked in the axial, coronal and sagittal planes, and special care is taken to ensure the x axis is correctly orientated. This is especially the case with data sets in Analyse format, where laterality is not clearly marked.
9.4.3.2 Paired images

With some modalities the results of processing are supplied with a co-registered space defining image. Examples include:

1. fMRI statistical parametric map showing task-related BOLD signal increases and mean EPI images
2. Processed tractography and FA map,
3. Regions of hypometabolism on FDG-PET and a space-defining CT image.

In these cases, the necessary transformation parameters can be determined for the space defining image, and then applied to the processed image.

9.4.4 Segmentation

9.4.4.1 Manual segmentation of regions of interest.

Any region of interest can be labelled in contiguous 2D slices using the segmentation editor tool to generate a 3D reconstruction. There are a number of standard tools to perform this task. Manual segmentation can be applied to building clearly defined anatomical structures and lesions, and also to building models based on functional imaging.

9.4.4.2 3D cortical segmentation

FreeSurfer is a third party brain imaging software package developed by the Athinoula A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital. It includes tools for the reconstruction of topologically correct and geometrically accurate models of grey/white and pial surfaces, for measuring cortical thickness, surface area and folding, and for computing inter-subject registration based on the pattern of cortical folds. In addition, an automated labelling of 35 non-cortical regions is included in the package. Processing an individual T1 weighted MRI takes around 20 hours.

Freesurfer is primarily used in this study to build a whole brain segmentation image, named the wmparc file, which is loaded onto AMIRA. The wmparc file is converted into a binary
image using Segmentation editor, and the resulting image is multiplied with the coregistered volumetric T1 image to derive a volumetric cortical mask.

**Figure 9-1 Image integration in AMIRA**

A- coregistration of two MRI images LEFT- pre-coregistration, RIGHT- post coregistration.

B- volume rendering of cortex.

C- Manual segmentation of cortically based lesion on coronal image (red)

9.4.4.3 3D vessel extraction

Segmentation editor and Arithmetic tool are used to generate a volume-grown, smoothed binary cortical mask that extends up to but not beyond the inner table of the skull vault. This mask is then applied to the 3D phase contrast MR or CT angiogram, using the Arithmetic tool, to remove unwanted extracranial vessels. The resulting image is surface-rendered
using the *Isosurface tool*. Further manual editing of the vessels can be performed using the *CreateSurface* tool, followed by *Surface editor*, to remove signal noise. Finally the *ScanConvertSurface* tool is required to restore the edited data set. In total this is a lengthy process (operator time 30-60 minutes), with substantial manual editing and significant difficulty extracting background noise without the loss of valuable data.

*Figure 9-2 3D vessel extraction*
A- 3D Surface rendering of intracranial and extracranial veins (cyan) from 3D phase contrast scan.
B- generation of vascular exclusion mask (red) overlaid on sagittal 3D phase contrast scan.
C- Application of vascular exclusion mask (red) to 3D surface rendering of vessels to separate intracranial (cyan) from extracranial (yellow).
D- 3D volume rendering of cortex with surface rendering of intracranial veins (cyan).
9.4.5 Data presentation and manipulation

The final resulting image shows a 3D volume rendering of the cortical surface, with volume or surface rendered clusters representing different modalities. These are colour-coded according to a fixed palette devised by NHNN, so that there is a common understanding amongst users on what the models represent. See table 9-4 below.

![3D volume rendering of brain in AMIRA with multiple modalities](image)

*Figure 9-3 3D volume rendering of brain in AMIRA with multiple modalities*  
*Volume rendering of cortex (grey) displayed in AMIRA software with the following associated modalities: focal cortical dysplasia (red), FDG-PET hypometabolism (purple), hand motor fMRI (green), corticospinal tractography (blue), veins (cyan).*

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Component</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Red</td>
<td>Green</td>
</tr>
<tr>
<td>Lesion</td>
<td>237</td>
<td>17</td>
</tr>
<tr>
<td>MEG</td>
<td>203</td>
<td>23</td>
</tr>
<tr>
<td>Language</td>
<td>244</td>
<td>126</td>
</tr>
<tr>
<td>Motor area</td>
<td>0</td>
<td>255</td>
</tr>
<tr>
<td>Sensory area</td>
<td>0</td>
<td>128</td>
</tr>
<tr>
<td>Veins</td>
<td>0</td>
<td>255</td>
</tr>
<tr>
<td>Arteries</td>
<td>186</td>
<td>44</td>
</tr>
<tr>
<td>White matter tracts</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td>EEG-fMRI</td>
<td>113</td>
<td>61</td>
</tr>
<tr>
<td>PET hypometabolism</td>
<td>130</td>
<td>0</td>
</tr>
</tbody>
</table>

See the table above for colour coding data.
Table 9-4 The colour palette to display 3DMMI in this study

<table>
<thead>
<tr>
<th>SPECT hyperperfusion</th>
<th>255</th>
<th>185</th>
<th>255</th>
<th>Pink</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanted electrodes</td>
<td>255</td>
<td>255</td>
<td>0</td>
<td>Yellow</td>
</tr>
<tr>
<td>Skull</td>
<td>224</td>
<td>224</td>
<td>224</td>
<td>White</td>
</tr>
</tbody>
</table>

9.4.6 Data export to neuronavigation system

The next step is the export of 3D models generated on AMIRA onto the Treon or S7 StealthStation for intra-operative use in ic-EEG. The feasibility of this approach in routine clinical practice was demonstrated in a pilot study by Rodionov (Rodionov et al., 2013). The pipeline to this final step of data transfer is outlined below.

An anatomical navigation MRI scan (T1 weighted with gadolinium) is obtained in the hours prior to surgery, with skin fiducials in situ on the patients head and scalp. This image is exported directly to the neuronavigation system, for the dual purpose of registering the patient head to the data sets, and to provide anatomical detail within the cortex.

This image is also imported onto the AMIRA network for the patient, and acts as a base with which to carry the different modalities in the form of homogenous binary labels. This image is not spatially transformed during further processing, to facilitate seamless co-registration with the working exam.

The navigation scan is upsampled or interpolated using the resample tool to improve the image resolution. Each modality is consecutively coregistered and resampled to this navigation scan using the affine registration and apply transformation tools. These data sets are converted into binary masks with appropriate thresholding, and then encoded into the navigation scan as a consecutive series of in-built 3D labels. This is achieved using the Arithmetic tool, and applying the equation:

\[
\text{Label} = A_{abs}(B-1) + xB
\]

\[A = \text{base image}\]
B = image carrying label

x = threshold to segment label (must be lower than maximum value in base image)

Since the binary masks are added on top of one another, they are added in an order to minimise the loss of important structural and functional data. The cortex mask is the first to be built, and the arteries and veins are the final masks to be built. The value of x is initially set above the maximum value of the navigation scan. With each added label the value of x should incrementally increase.

The obvious disadvantage to this approach is that each ‘voxel’ can only be assigned to one mask. In practice this can result in serious distortions to the modelling of the cortical surface.

The completed image is cleaned of identifying information and then exported in DICOM format to the neuronavigation system.

9.4.7 Building models on StealthStation

At NHNN, the Medtronic Treon and S7 StealthNavigation systems are used. The binary models study is first loaded on the system as the reference exam. Each modality is then rebuilt by thresholding using the StealthNavigation Build Models tool. This gives an image with labelled masks but no anatomical detail by which to navigate the brain.

The navigation image is loaded as the working exam, and then co-registered with the reference exam. The resulting image displays both the crucial anatomic detail of the working exam, and the attached 3D labels of the reference exam.
Figure 9-4 Data export to neuronavigation system
A, B, C- surface rendered binary models of scalp, cortex and blood vessels in AMIRA
D- axial STEALTH MRI scan displayed in S7 stealthstation,
E- axial binary models image displayed in S7 stealthstation,
F- 3D model of cortex, veins and segmented lesion in S7 stealthstation

9.4.8 Post-operative data integration

Following implantation of ic-EEG, the localisation of electrode contacts relative to structural and functional data can be examined by reconstructing the electrodes on the 3DMMI using AMIRA. Post-operative CT imaging is entered into the AMIRA network and coregistered to the T1 image. The electrode contacts are displayed using Isosurface, and segmented by a combination of thresholding and use of Surface editor. This is the preferred option for visualising electrodes post-implantation.

In a similar fashion post-operative MRI can be integrated into the 3DMMI using AMIRA to demonstrate the actual end position of implantation with brain shift. This can only be done if there is an acceptable minimum distance between adjacent contact electrodes to avoid induction of current in the MRI suite that could result in heating, which is dependent on each unit’s own safety regulations.
Figure 9-5 Post-operative visualisation of implanted electrodes
A- 3D volume rendering of cortex in AMIRA with surface rendered depth electrodes (external views).
B- 3D volume rendering of scalp, cortex, veins and depth electrodes in the S7 stealthstation, with planned trajectories overlaid (external views).

9.5 EpiNav™ software

9.5.1 Aims
The aims for the development of EpiNav™ are to generate specialised software for multimodality image integration, advanced 3D visualisation and epilepsy surgery planning. The emphasis is on ease of use in a clinical scenario, allowing real time use of software by clinicians, and rapid incorporation into the clinical pipeline. We anticipate that over the
course of software development EpiNav™ will replace AMIRA as the tool for image integration and epilepsy surgery planning in clinical practice. We also aim to disseminate EpiNav™ to other centres both in the UK and in Europe under confidentiality agreements as laid out by UCL and Medtronic.

9.5.2 Funding

EpiNav™ is trademarked by UCLBusiness PLC and UCL. It is being developed in close collaboration with Medtronic, as required by the Health Innovation Challenge Fund grant that requested an industry partnership. Any Intellectual Property arising from the collaboration is owned by UCL in the first instance. The author has no financial interests in the development of EpiNav™. Due to the model of funding it is not possible to offer EpiNav™ as open source software at the present time. However, we are always looking for other centres to trial EpiNav™, under confidentiality agreements as previously mentioned.

9.5.3 Development

EpiNav™ is being developed by Prof Sebastien Ourselin’s group at the Centre of Medical Imaging and Computing (CMIC), UCL, London. The software runs on the NifTK platform, a translational imaging platform that combines NiftyReg, NiftySeg and NiftyView (Clarkson et al., 2014). Development is undertaken in collaboration with Medtronic, for compatibility with the Medtronic StealthStations in the operating theatre.

Development is divided into two phases.

9.5.3.1 Phase 1

Phase 1 describes the core requirements for the software, to reproduce the functionality of AMIRA. Phase I also includes a trajectory planning module, and a simplified pipeline for export of plans to the operating theatre. The requirements of Phase I are shown below.

1. Import images in DICOM and Nifti format
2. View the images in a viewfinder with orthogonal and 3D windows

3. Perform automated rigid body co-registration of images to T1 image

4. 2D/3D Segmentation Tools

5. Automatic segmentation of blood vessels from dedicated vascular imaging

6. Single electrode manual planning tools

7. Export module for transferring models and plans in archive format to Medtronic Stealthstation

9.5.3.2 Phase 2

Phase 2 describes new innovations that are to be added to the EpiNav™, following feedback from the clinicians. The priority is to develop forms of computer-assisted planning, which will complement the clinical uptake of SEEG in our unit. The development of computer-assisted planning (CAP) is described in detail elsewhere (Zombori et al., 2014), and the necessary data preparation is detailed later in this chapter.

9.6 Image integration on EpiNav™

9.6.1 Viewer display

The basic viewer “Display” is demonstrated in Figure 9-6 with a 2x2 window display, showing orthogonal and 3D views. The size of the windows can be manually adjusted by dragging the borders and the contrast can be adjusted by clicking on the bar to the right of the viewer.

Data manager is located on the far left. This demonstrates the list of loaded images, and is where further processed images appear. This is also where the user selects which images they are currently viewing and working on. The checkbox to the left of the image name allows the user to show/hide the image in the viewer. The data manager functions in a
hierarchical fashion with images higher up the list consecutively placed over one another in the viewer display.

The available image processing tools are represented as speed buttons (icons) in a row above the windows. Clicking a specific speed button visualises the corresponding panel containing control elements for this tool on the right side of the viewer.

The basic functions are similar to other neuroimaging viewers. The user can zoom in and out of the image at any particular centre point, scroll through slices, and rotate the data set in the 3D window.

9.6.2 Loading images

To load images the supported data formats are DICOM and Nifti. The user can import data using ‘drag and drop’, by accessing the main menu “File/Open” or by a speed button (icon) “Open”.

Figure 9-6 Basic viewer of EpiNav™
LEFT- Datamanager, TOP- speed buttons for plug in tools, RIGHT- current plug in tool in use
9.6.3 Coregistration

Rigid body registration is performed using the *NiftyReg* plug in. The user selects the reference and floating image, and runs the automated tool. The result is a Nifti file of the floating image, coregistered and resampled to the reference image. A txt file is also created that specifies the parameters of transformation. This can be used in the event of coregistering paired images, using the *RegResample* tool. The quality of the coregistration can be assessed by viewing both the Nifti file generated by *NiftyReg* over the reference image, and then altering the transparency of the former.

9.6.4 Segmentation and 3D visualisation

Segmentation of an image can be done either manually using the advanced *Segmentation Editor*, or by thresholding an image using the *Basic Processing Tools*. A data set can be visualised as a 3D surface rendered stereolithography (stl) file using either the *Surface Extractor* plug in, where the maximum threshold is defined, or as a smooth polygon surface direct from the *Data Manager*.

![Figure 9-7 Segmentation and 3D visualisation in EpiNav™](image)

*Figure 9-7 Segmentation and 3D visualisation in EpiNav™*

A- axial T1 MRI with superimposed surface models
B- 3D surface rendering of models (cyan-veins, green- motor hand from transcranial magnetic stimulation, orange- arcuate fasciculus tractography, blue- corticospinal tractography, pink- optic radiation tractography, yellow- uncinate fasciculus tractography, purple- thalamus segmentation)
9.6.5 Vessel extraction

Vessel extraction is performed using the *Vesselness* tool, which is described in detail elsewhere (Zuluaga et al., 2014). For best results, the user should apply *Vesselness* to the data set in native space, before applying the parameters of coregistration generated using *NiftyReg* and *RegResample*. Following coregistration of the results of *Vesselness*, it is then necessary to apply a cortical mask to filter out extracranial blood vessels. The surface rendering is thresholded to remove noise whilst preserving valuable data, and saved as an stl file. The final step is to process the stl file in Meshlab software, manually removing isolated pieces that represent noise. The resulting stl file is then reimported into the EpiNav™ network as the final vascular model.

This process is performed on 3D phase contrast MRI to visualise veins, and on CT angiography to visualise arteries. It can also be performed on Stealth T1 MRI with gadolinium to visualise both arteries and veins although there remains some noise at the cerebral convexities.

![Figure 9-8 Vessel extraction in EpiNav](image)

*A-* Axial CT angiogram coregistered with 3D phase contrast MRI.
*B-* 3D surface rendering of veins (cyan) and arteries (red)

9.6.6 Planning

9.6.6.1 Manual planning
Manual planning is a phase I requirement in the development of EpiNav™. Using the first generation planning tool, the user can create a plan with multiple trajectories by consecutively selecting targets and entry points to generate individual trajectories. For each trajectory a ‘probes eye viewer’ that visualises the data sets at a plane perpendicular to the trajectory can be used to ensure a suitable avascular path.

9.6.6.2 Computer-assisted planning (CAP)
CAP is a phase II requirement in the development of EpiNav™. The aim is to improve speed, safety and grey matter capture in the generation of plans of trajectories. Our group started by optimising single trajectories and then moved to an automated multi-trajectory planner. The development of CAP is described in detail elsewhere (Zombori et al., 2014).

CAP depends on a number of surface renderings being present in the EpiNav™ network. For each patient, the following surface renderings are required:

1. Vascular structures
2. Surface sulci
3. Cortex
4. Grey matter
5. Scalp
6. Scalp inclusion mask

The generation of vascular structures has been discussed previously.

Surface sulci, cortex and grey matter structures are all generated using the Freesurfer software.

Grey matter is represented in the ribbon.mgz file. The mgz file is converted to nifti format, imported into EpiNav™, coregistered and surface rendered. Cortex is generated from the
wmparc.mgz file. The mgz file is converted to nifti format, imported into EpiNav™, coregistered, thresholded to include all data (values 1-5002), and then surface rendered. See figure 9-9.

Figure 9-9 Generation of cortex and grey matter surface models
A- axial view of wmparc file, B- wmparc file thresholded from 1-5002, C- surface rendering of binarised wmparc file. D- axial T1 MRI with coregistered ribbon file, E- ribbon file, F- surface rendering of ribbon file

Surface sulci are generated from the wmparc.mgz file. This is a multi-step process, performed using the Basic Image Processing tools in Epinav™, outlined below. These include a closing function, that fills volumetric holes in data sets, and a reduction function, that performs a voxel specific volumetric reduction in data sets. The resulting data sets are coregistered and surface rendered.

Generation of Whole Sulci:

Whole sulci = Image A - Image B
Image A is wmparc file, binarised and closed by 3

Image B is wmparc file, binarised

![Image A: WMPARC file, binarised and closed by 3](image1)

![Image B: WMPARC file, binarised](image2)

**Figure 9-10 Generation of Whole Sulci**

Generation of Surface Sulci:

Surface sulci= Whole Sulci x Image C

Image C is wmparc file, binarised, closed by 3, reduced by 3, inverted

![Image C: WMPARC file, binarised, closed by 3, reduced by 3, inverted](image3)

**Figure 9-11 Generation of surface sulci**

Scalp and scalp inclusion masks are generated from the T1 navigation MRI. The data set is simplified by a Gaussian transformation, and surface rendered using the Surface extractor tool. The resulting data set is transferred to MeshLab as an stl file, and cleaned of all isolated pieces to give a surface rendering of the scalp with no intracranial contents. The manual editing tools allow the user to custom build a scalp inclusion mask from this in MeshLab, removing the face, ear, region below the transverse sinus and the contralateral...
hemisphere. Both the scalp and the scalp inclusion masks are then reloaded into the Epinav™ network.

*Figure 9-12 3D visualisation in EpiNav™*

3D visualisation of scalp (white), scalp inclusion mask (yellow), cortex (pink), veins (cyan), arteries (red) and surface sulci (green) in EpiNav™

9.6.7 Export to StealthStation

Using the S7 Export plug in, the export of models and plans to an archive format that is recognised by the Stealthstation is straightforward. The user selects a DICOM image of the navigation T1 MRI as the reference image to carry the required models and plans. The user then specifies the destination of the archive and runs the export module.

The resulting file can be uploaded onto a universal serial bus (USB) stick for transfer to the StealthStation. This is a more simple and streamlined approach to data export compared with the process using AMIRA.
10 How widespread is the use of 3D Multimodality Integrated Models in Epilepsy Surgery practice?

10.1 Introduction

3DMMI is ideally suited to the planning of epilepsy surgery since the practice requires the simultaneous analysis of multiple data sets and the consideration of how each data set relates to another in 3D space.

Uses of 3DMMI in epilepsy surgery include but are not limited to:

1. Identification of complex gyral anatomy in a brain model
2. Placement of structural and functional regions of interest on an anatomically detailed brain model
3. Optimal evaluation of the spatial concordance within the presumed EZ established using different structural and functional modalities
4. Unmasking of previously cryptogenic lesions using postprocessing methods
5. Determination of the relationship between the presumed EZ and the functional deficit zone
6. Identification of complex vascular anatomy
7. Reconstruction of implanted electrodes and their relationship to underlying anatomical and functional models

The use of 3DMMI in epilepsy surgery is well described in the literature (Hogan et al., 1999, Murphy et al., 2001, Murphy et al., 2004, Wellmer et al., 2010, Morales-Chacon et al., 2015). We have previously demonstrated in our unit that the routine use of 3DMMI in a busy epilepsy surgery practice is feasible and carries value (Rodionov et al., 2013).
Although the consensus appears to support the routine use of 3DMMI in this field, there is very little known on how widespread the uptake of this technique is in centres around the world. A PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) using the keywords ‘Multimodality’ AND ‘Epilepsy Surgery’ generates 136 results (June 2015), but there is no reference to the current uptake of these methods in clinical practice.

The aim of this chapter is to explore whether 3DMMI remains a tool for specialist centres with interests in research, or whether it has translated to routine clinical practice. As a secondary aim, we examine the unmet need for software that facilitates image integration and visualisation, with a view to informing the development of our own EpiNav™ software package.

10.2 Method

A simple questionnaire was developed and distributed using the SurveyMonkey website (www.surveymonkey.com). SurveyMonkey is a web survey development cloud-based company. The questionnaire was designed to record the current uptake of 3DMMI in the practice of epilepsy surgery, the methods of implementation and the barriers to further uptake.

Experts in epilepsy surgery from a number of specialties and from a number of countries were invited to participate.

The questionnaire was circulated in the following ways:

1. Email invitation to named Neurosurgeons based in the UK with a specialist interest in Epilepsy Surgery

2. WFNS e-blast system

3. Email invitation to named chapters in the ILAE

The questionnaire was composed of 9 questions and is reproduced in the appendix.
10.3 Results

The questionnaire was emailed to 18 named Consultants in the UK and to 86 chapters of the ILAE. This makes a total of 104 personal invitations to the questionnaire. Furthermore, the e-blast invitation on the WFNS website will have captured additional people.

10.3.1 Respondents

Respondents to the questionnaire were anonymised. In total there were 40 responses.

There were 8/40 (20%) respondents from the UK, 8/40 (20%) from Europe, 3/40 (7.5%) from the United States and 21/40 (52.5%) from the rest of the world.

The majority of the respondents were neurosurgeons (31/40, 77.5%), with neurologists (7, 17.5%), a neurophysiologist and a neuroradiologist making up the rest.

10.3.2 Multimodality imaging and integration

The reported imaging modalities used in presurgical evaluation and surgical treatment are shown in table 10-1.

In total, 8/40 (20%) respondents reported using 3DMMI. 4/8 (50%) of these came from the UK, compared with 1/8 (12.5%) respondents in Europe, 1/3 (33.3%) respondents in US and 2/19 (10.5%) respondents in the rest of the world. Different software packages were used by each respondent, aside from the Analyze software package (Mayo Clinic Biomedical Imaging Resource) that was used in two cases.
<table>
<thead>
<tr>
<th>Modality</th>
<th>UK responses</th>
<th>Outside UK responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical MRI</td>
<td>8/8 (100%)</td>
<td>30/32 (93.8%)</td>
</tr>
<tr>
<td>Language fMRI</td>
<td>8/8(100%)</td>
<td>18/32 (56.3%)</td>
</tr>
<tr>
<td>Motor fMRI</td>
<td>7/8 (87.5%)</td>
<td>16/32 (50%)</td>
</tr>
<tr>
<td>Tractography</td>
<td>7/8 (87.5%)</td>
<td>17/32 (53.1%)</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>6/8 (75%)</td>
<td>16/32 (50%)</td>
</tr>
<tr>
<td>Ictal SPECT</td>
<td>6/8(75%)</td>
<td>16/32(50%)</td>
</tr>
<tr>
<td>MEG</td>
<td>5/8 (62.5%)</td>
<td>3/32 (9.4%)</td>
</tr>
<tr>
<td>CT angiogram (CTA)</td>
<td>5/8 (62.5%)</td>
<td>13/32 (40.6%)</td>
</tr>
<tr>
<td>Magentic resonance venogram (MRV)</td>
<td>5/8 (62.5%)</td>
<td>11/32 (34.4%)</td>
</tr>
<tr>
<td>ESI</td>
<td>4/8 (50%)</td>
<td>18/32 (56.3%)</td>
</tr>
</tbody>
</table>

Table 10-1 Questionnaire responses on the Imaging modalities used in the presurgical evaluation and surgical treatment of epilepsy

![Diagram](image)

*Figure 10-1 Range of software packages used for image integration amongst the respondents*
Of the respondents who have adopted 3DMMI, the way they use the models in clinical practice is shown in Table 10-2.

<table>
<thead>
<tr>
<th>Use</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guide decision making</td>
<td>8/8 (100%)</td>
</tr>
<tr>
<td>Guide cortical resections</td>
<td>7/8 (87.5%)</td>
</tr>
<tr>
<td>Communication between doctor and patient</td>
<td>5/8 (62.5%)</td>
</tr>
<tr>
<td>Implementation of intracranial electrode implantation</td>
<td>5/8 (62.5%)</td>
</tr>
<tr>
<td>Post operative reconstruction of implanted electrodes</td>
<td>4/8 (50%)</td>
</tr>
<tr>
<td>Communication between health care team</td>
<td>4/8 (50%)</td>
</tr>
</tbody>
</table>

*Table 10-2 Questionnaire responses on how 3DMMI is used in clinical practice*

10.3.3 Barriers to adopting 3DMMI

The main barriers to adoption of 3DMMI appear to be the financial cost and expertise needed for image integration. See table 10-3.

<table>
<thead>
<tr>
<th>Barriers to adoption</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial cost for image integration</td>
<td>21/32 (65.6%)</td>
</tr>
<tr>
<td>Availability of modalities</td>
<td>13/32 (40.6%)</td>
</tr>
<tr>
<td>Expertise needed for image integration</td>
<td>12/32 (37.5%)</td>
</tr>
<tr>
<td>Time taken to achieve image integration</td>
<td>6/32 (18.8%)</td>
</tr>
<tr>
<td>Not felt to be clinically useful</td>
<td>3/32 (9.4%)</td>
</tr>
<tr>
<td>In progress</td>
<td>2/32 (6.3%)</td>
</tr>
</tbody>
</table>

*Table 10-3 Questionnaire responses on the barriers to adopting 3DMMI*
However, in principle image integration was viewed positively by most respondents both inside and outside the UK. See table 10-4.

<table>
<thead>
<tr>
<th>Usefulness of 3DMMI in principle</th>
<th>UK</th>
<th>Outside UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very useful</td>
<td>6/8 (75%)</td>
<td>22/32 (68.8%)</td>
</tr>
<tr>
<td>Slightly useful</td>
<td>2/8 (25%)</td>
<td>5/32 (15.6%)</td>
</tr>
<tr>
<td>Neutral</td>
<td>0/8</td>
<td>4/32 (12.5%)</td>
</tr>
<tr>
<td>Not particularly useful</td>
<td>0/8</td>
<td>1/32 (3.1%)</td>
</tr>
<tr>
<td>Not useful at all</td>
<td>0/8</td>
<td>0/32</td>
</tr>
</tbody>
</table>

*Table 10-4 Questionnaire responses on the usefulness of 3DMMI in principle*

The three factors that would most likely make the respondents use 3DMMI in their future clinical practice was availability of software (27/40), ease of use (26/40) and cheap cost of implementation (25/40). 2/40 respondents reported that they would not use 3DMMI in any circumstances.

10.4 Discussion

10.4.1 Summary

The main finding of this questionnaire is that the use of 3DMMI in epilepsy surgery is not routine clinical practice. Of the 40 respondents, only 8 reported the use of 3DMMI in their practice.

Low uptake of 3DMMI is perhaps not surprising in the developing world, where the costs can be prohibitive. There were 2 reports of the use of 3DMMI outside the UK, Europe and the US; this was in Algeria and Columbia.
However, a mixed picture emerges in the wealthier developed countries. In the UK the uptake was 4/8 and in Europe was 1/8. Interestingly even in the US, where cost is less important, only 1/3 respondents reported the use of 3DMMI. These findings support the notion that 3DMMI is a tool that is considered a useful research add-on but not currently essential in routine clinical practice worldwide.

The second finding in this study is that 3DMMI is implemented in numerous ways with no consensus on the single best software. This is perhaps not surprising when one considers that epilepsy surgery is a heterogeneous subspecialty with a range of options on how to implement ic-EEG. These include:

- Frame-based versus frameless techniques
- Use of robotic placement
- Subdural grid implantation versus SEEG
- Choice of neuronavigation systems

The integration softwares used include both commercially available systems and nonspecialised softwares that are open source. There is no reported use of StealthViz, the data integration software of the market leaders in neuronavigation, Medtronic.

There is more consensus amongst users on how the 3D multimodal data sets are used in clinical practice. 8/8 use the models to guide decision-making and 7/8 use the models to guide cortical resections. This suggests that the models are used in ‘end-stage’ neuronavigation systems in the operating theatre, and help tailor resections.

Fewer groups report using the models earlier on in the presurgical evaluation, either as a communication tool to patients (5/8) or colleagues (4/8), or to implement intracranial implantations (5/8). This may be due to 2 reasons: either the models are not presented earlier on in the presurgical evaluation, and only generated for the purposes of
neuronavigation during surgery, or there is an under-reporting of their presurgical use. The second possibility should be considered as neurologists and neurophysiologists are under-represented in the response rate (9/40), and neurosurgeons are more likely to report their own use of the technology.

Interestingly only 4/8 groups report post-operative CT reconstruction of the implantation electrodes. This is a relatively straightforward technique that is easy to implement, and has been widely reported in the literature. Our own group feel there is significant benefit with this technique in the interpretation of the intracranial contact recordings and their relationships to anatomical structures.

The third finding from the questionnaire is an understanding on why most groups currently do not use 3DMMI in clinical practice. The main barrier to use of 3DMMI seems to be the financial cost of implementation (21/32) and expertise required (12/32). The current situation is that 3DMMI can be expensive to run. Start-up costs include purchasing the necessary software and licensing to use the software and training in how to use the software. Running costs include personnel to perform the image integration. In centres where 3DMMI is currently used, no data was collected on who performs the data integration. However, it is likely that this is done by a member of the team with a specialist interest in multimodality imaging or by a research fellow engaged in a higher degree. With current software limitations routine adoption of 3DMMI would probably require the employment of additional personnel to perform the integration. It is also worth noting that image integration is, at the present time, a complex process. The user has to be fluent in a range of different software platforms, and has to organise his/her own pipeline to generate clinically useful images. This is difficult to reproduce in different centres, perhaps explaining in part why this tool has failed to gain widespread uptake.

Availability of modalities was also reported as a barrier to adoption in some cases (13/32).
Groups using 3DMMI unsurprisingly had a higher number of modalities at their disposal. It is possible the complex interplay between increasing numbers of data sets drove the need for placing these data sets within an integrated 3D model. Alternatively, it is possible that the number of modalities is not a driver for this technology, and that centres engaged in research modalities are more likely to be simultaneously engaged in multimodality integration.

The final point from the replies is that the respondents as a group felt very positive towards the concept of 3DMMI, and there was a general wish to implement this in the future. 28/40 deemed 3DMMI as very useful and 7/40 deemed 3DMMI as slightly useful in the practice of epilepsy surgery. In contrast 4/40 were neutral and 1/40 deemed 3DMMI as not particularly useful. This respondent was a neurosurgeon from Egypt, who reported using only anatomical MRI in the presurgical evaluation.

Whilst there is a general wish to implement 3DMMI, there remain significant barriers as previously discussed. When respondents were asked what would make them more likely to adopt 3DMMI, the response was clear. Availability of software, ease of use and cost of implementation were the three biggest factors by far, with no difference between them. This was evenly distributed across the UK, Europe, the US and elsewhere.

10.4.2 Limitations

It is difficult to quantify the overall response rate for this questionnaire, as it was posted online. However, the response rate for emailed invitations was poor, with 8/18 (44%) respondents from UK epilepsy surgery centres replying.

As previously discussed, there is an over-representation of views from neurosurgeons in the replies, with 31/40 respondents identifying themselves as neurosurgeons. This is likely to give a bias towards the surgical use of 3DMMI in clinical practice.
Finally there is the possibility of a responder bias in this questionnaire, with respondents being more positive towards 3DMMI than other professionals in Epilepsy Surgery who chose not to complete the questionnaire. This may give a skewed picture on the question of how useful 3DMMI is considered in clinical practice. However, even taking this into account it is clear that the uptake of 3DMMI is lower than previously considered in the UK and Europe. There were only 3 replies from North American centres, 1 of which reported the use of 3DMMI. More feedback from the US would be useful, as it is likely this is the biggest market for 3DMMI in epilepsy surgery.

Whilst the low response rate means the views expressed here cannot be deemed representative of the entire cross-specialty, it is to date the only record of the current state of 3DMMI in epilepsy surgery.

10.5 Conclusion

This questionnaire supports the position that 3DMMI is useful in epilepsy surgery, is positively viewed by neurosurgeons and is underutilised in clinical practice. The main barriers to implementation are cost and expertise. Although there are several limitations to this survey data, there appears to be a market for dedicated software for image integration, 3D visualisation and surgical planning in epilepsy surgery with emphasis on ease of use and low cost.
11 Utility of 3D multimodality imaging in the implantation of intracranial electrodes in epilepsy*

11.1 Introduction

Intracranial-EEG is indicated in patients with medically intractable focal epilepsy, when non-invasive investigations have failed to adequately define the EZ (Blount et al., 2008). The decision to proceed to ic-EEG, and the precise location and configuration of the implantation arises from a multi-disciplinary case review with all the non-invasive investigations. ic-EEG may take the form of subdural grid electrodes, a combination of grid and depth electrodes, and by stereoelectroencephalography (SEEG).

3DMMI in epilepsy surgery is well established in the research literature and is routinely applied to patients undergoing presurgical evaluation at the NHNN (Rodionov et al., 2013). However, the previous chapter demonstrated that this is not standard practice in other centres with barriers to adoption including cost and expertise.

The aim of this study is to validate the use of 3DMMI in clinical practice with a large prospective cohort and demonstrate how it can be used throughout presurgical evaluation.

11.2 Method

11.2.1 Recruitment

All individuals with medically refractory focal epilepsy, undergoing presurgical evaluation for ic-EEG and possible subsequent neocortical resection between August 2012 and August 2014, were invited to participate in the study.
11.2.2 Image integration

Relevant structural and functional image acquisition was based entirely on clinical need, as determined by the patient’s consultant neurologist, following discussion and consensus at the weekly Multidisciplinary Team Meeting.

Patients undergoing ic-EEG underwent a T1-weighted Stealth MRI scan with gadolinium for the purposes of neuronavigation, and a 3D phase contrast MRI scan for the purposes of visualising cortical surface vein anatomy. Individuals having SEEG also had a CTA to visualise intracerebral arteries.

All available structural and functional imaging modalities performed in the patient’s presurgical evaluation were stored on a single workstation. Data pre-processing was performed locally when required prior to transfer to the workstation for the purpose of image integration.

Image integration was performed using the AMIRA (Version 5.4.0, Visualization Sciences Group, Massachusetts, US) software package and more recently the Epinav™ (CMIC, UCL, London) software package. Image integration is a stepwise process by which each new modality is co-registered with the base anatomical image (Stealth T1-weighted MRI with gadolinium injection), and display settings are adjusted using a range of tools to offer optimal data presentation and visualisation (See chapter 9 for more details).

The final multimodal image is a 3D volume rendered representation of the brain, with volume or surface rendered clusters representing different modalities. The user can manipulate the final multimodal image in a number of ways, including alteration of the transparency of the brain and different modalities, rotation of the image in any plane and changing the scaling of the image.

The data are presented at Multi-Disciplinary Team Meetings, where the overall strategy of implantation (strategy) are decided, and at surgical meetings, where precise implantation details (planning) are decided. Once both the strategy and detailed planning are completed
and approved by both neurophysiologist and operating neurosurgeon the 3D models generated on AMIRA/EpiNav™ are exported onto the S7 Stealthstation for intra-operative use during the implantation of ic-EEG electrodes. Increasingly image integration and surgical planning has been performed on the EpiNav™ software in our centre. EpiNav™ is an easy to use custom built software package dedicated to strategy and planning in epilepsy surgery. Like AMIRA, EpiNav™ can be used for rapid image integration and 3D visualisation. In addition to this, EpiNav™ has added functionality, including a trajectory planner module for the placement of depth electrodes and a dedicated export module for archiving models and plans directly onto the S7 StealthStation (Table 11-1).

<table>
<thead>
<tr>
<th></th>
<th>AMIRA</th>
<th>EpiNav™</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Availability</strong></td>
<td>Commercial software, license required</td>
<td>In-house software, In development</td>
</tr>
<tr>
<td><strong>Technical skills needed</strong></td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td><strong>User friendliness</strong></td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Duration of processing</strong></td>
<td>2-3 hours</td>
<td>1-2 hours</td>
</tr>
<tr>
<td><strong>Visualisation</strong></td>
<td>Volume-rendering</td>
<td>Surface-rendering</td>
</tr>
<tr>
<td><strong>Vessel extraction</strong></td>
<td>Multi-step</td>
<td>Single step</td>
</tr>
<tr>
<td><strong>Planning</strong></td>
<td>Not available</td>
<td>Trajectory planning module</td>
</tr>
<tr>
<td><strong>Export to S7 Stealthstation</strong></td>
<td>Difficult</td>
<td>Easy</td>
</tr>
<tr>
<td><strong>Post-operative electrode reconstructions</strong></td>
<td>Easy</td>
<td>Easy</td>
</tr>
</tbody>
</table>

*Table 11-1 Comparison of AMIRA and EpiNav software packages
*not inclusive of data collation and pre-processing
Following implantation of electrodes, the localisation of electrode contacts relative to structural and functional data can be examined by reconstructing the electrodes on the 3DMMI using AMIRA/EpiNav™. Post-implantation CT imaging is coregistered to the T1 image (Figure 11-1).

Figure 11-1 Example of 3DMMI in AMIRA for planning grid implantation
A- LEFT: Volume rendering of cortex (grey) with addition of motor fMRI activation (green) and vein segmentation (cyan) in the context of the craniotomy bone flap, visualised by CT reconstruction. RIGHT: Intra-operative photograph to show cortical surface and overlying vascular structures.
B- LEFT: Addition of subdural grids, with reconstruction on AMIRA. RIGHT intra-operative photograph to show positioning of subdural grids on cortical surface

11.2.3 Planning process

Two ‘milestone’ discussions were identified in all patients undergoing consideration of ic-EEG. The first is the implantation strategy and the second is the precise surgical planning (Figure 11-2).
11.2.3.1 Implantation Strategy
The Implantation Strategy is the definitive decision on whether to proceed to ic-EEG, directly proceed to resective surgery or abandon the possibility of surgical treatment. In the cases of ic-EEG, a further decision is made on the favoured strategy of using subdural grids electrodes, depth electrodes or a combination of both, and how the desired coverage could be achieved. This meeting typically takes place a number of months prior to implantation. The Implantation Strategy is primarily determined by Clinical Neurophysiologists and Neurologists in a case-centred meeting. The presurgical evaluation, video telemetry and neuroimaging are reviewed and a discussion takes place, led by the Neurophysiologists, on how best to proceed. Following consensus on the implantation strategy, the 3DMMI is disclosed to the group using the AMIRA workstation/Epinav™ workstation, and/or the S7 StealthStation. Any additional insights, and any changes to the agreed strategy, are recorded. The primary endpoint is whether disclosure of 3DMMI changes Implantation Strategy.

11.2.3.2 Precise Surgical Planning
The Precise Surgical Planning specifies the implementation of the ic-EEG. It is carried out by the Consultant Neurosurgeon and a Neurosurgical trainee, and is performed on the EpiNav™ workstation and/or S7 Stealthstation (AMIRA has no surgical planning functionality). This typically takes place one week before the implantation. The Precise Surgical Planning consists of planning trajectories for the insertion of depth electrodes, the identification of cortical anatomy and the planning of subdural grid placement. Following completion and documentation of the provisional plan, 3DMMI is disclosed on the EpiNav™ workstation/Neuronavigation system, with the models displayed in 3D and also as contours on the orthogonal plane viewfinder. Any changes to the provisional plan are recorded. These may include changes in electrode arrangement, changes in electrode entry and target points, and changes to grid positioning. The primary endpoint is whether disclosure of 3DMMI changes the Precise Surgical Planning.
11.3 Results

11.3.1 Demographics

Table 11-2 demonstrates the demographics and overall results of the 54 patients in the study
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Epilepsy duration (yrs)</th>
<th>Radiological Lesion</th>
<th>Description</th>
<th>Presumed EZ</th>
<th>Grid v depth</th>
<th>Software</th>
<th>Strategy change</th>
<th>Precise surgical planning change</th>
<th>Complications</th>
<th>Outcome</th>
<th>ILAE outcome(12/12)</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45F</td>
<td>30</td>
<td>Yes</td>
<td>L STG cavernoma, HS</td>
<td>L temporal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>4</td>
<td>HS</td>
</tr>
<tr>
<td>2</td>
<td>16M</td>
<td>4</td>
<td>No</td>
<td>NA</td>
<td>L frontal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>NR</td>
<td>N</td>
<td>Subdural haematoma</td>
<td>Cortical resection</td>
<td>3</td>
<td>NAD</td>
</tr>
<tr>
<td>3</td>
<td>31M</td>
<td>18</td>
<td>Yes</td>
<td>FCD</td>
<td>R frontal</td>
<td>SEEG</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>NAD</td>
</tr>
<tr>
<td>4</td>
<td>33F</td>
<td>23</td>
<td>Yes</td>
<td>FCD</td>
<td>R parietal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>FCD type IIB</td>
</tr>
<tr>
<td>5</td>
<td>41M</td>
<td>16</td>
<td>Yes</td>
<td>heterotopia, HS</td>
<td>R temporal/parietal</td>
<td>SEEG</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>HS</td>
</tr>
<tr>
<td>6</td>
<td>25M</td>
<td>10</td>
<td>No</td>
<td>NA</td>
<td>L temporal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>Cortical gliosis</td>
</tr>
<tr>
<td>7</td>
<td>27M</td>
<td>17</td>
<td>No</td>
<td>NA</td>
<td>L parieto-occipital</td>
<td>SEEG</td>
<td>EpiNav</td>
<td>NR</td>
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<td>Nil</td>
<td>Excluded</td>
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</tr>
<tr>
<td>8</td>
<td>19F</td>
<td>10</td>
<td>Yes</td>
<td>Encephalomalacia</td>
<td>R occipital</td>
<td>SEEG</td>
<td>EpiNav</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Declined further treatment</td>
<td>4</td>
<td>FCD type IIB</td>
</tr>
<tr>
<td>9</td>
<td>43M</td>
<td>29</td>
<td>Yes</td>
<td>FCD</td>
<td>R temporal</td>
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<td>EpiNav</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
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<td>FCD type IIB</td>
</tr>
<tr>
<td>10</td>
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<td>Yes</td>
<td>FCD</td>
<td>L peri-rolandic</td>
<td>Grids</td>
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<td>N</td>
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<td>FCD type IIB</td>
</tr>
<tr>
<td>11</td>
<td>38F</td>
<td>31</td>
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<td>FCD</td>
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<td>AMIRA</td>
<td>N</td>
<td>NA</td>
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<td>12</td>
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<td>30</td>
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<td>Y</td>
<td>Nil</td>
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<td>60F</td>
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<td>L frontal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>NR</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>4</td>
<td>DNET</td>
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<td>Grids</td>
<td>AMIRA</td>
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<td>Y</td>
<td>Nil</td>
<td>Excluded</td>
<td>3</td>
<td>DNET</td>
</tr>
<tr>
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<td>27F</td>
<td>24</td>
<td>E</td>
<td>FCD</td>
<td>L frontocentral</td>
<td>Grids</td>
<td>AMIRA</td>
<td>N</td>
<td>N</td>
<td>Infection</td>
<td>Cortical resection</td>
<td>1</td>
<td>FCD type IIA</td>
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<td>39M</td>
<td>36</td>
<td>Yes</td>
<td>Cavernoma</td>
<td>L superior parietal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>N</td>
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<td>Nil</td>
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<td>Cavernoma</td>
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<td>22</td>
<td>No</td>
<td>NA</td>
<td>L anterior frontal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>N</td>
<td>N</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>4</td>
<td>FCD type IIA</td>
</tr>
<tr>
<td>18</td>
<td>49M</td>
<td>35</td>
<td>Yes</td>
<td>DNET</td>
<td>L frontal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>Y</td>
<td>NR</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>4</td>
<td>DNET</td>
</tr>
<tr>
<td>19</td>
<td>23F</td>
<td>15</td>
<td>Yes</td>
<td>FCD</td>
<td>L frontal</td>
<td>Grids</td>
<td>AMIRA</td>
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<td>N</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>3</td>
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<tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>20</td>
<td>28M</td>
<td>21</td>
<td>Yes</td>
<td>FCD</td>
<td>L parietal</td>
<td>Grids</td>
<td>AMIRA</td>
<td>Y</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
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<td>FCD type IIB</td>
</tr>
<tr>
<td>21</td>
<td>47M</td>
<td>41</td>
<td>Yes</td>
<td>FCD</td>
<td>L frontal</td>
<td>Not done</td>
<td>AMIRA</td>
<td>Y</td>
<td>ND</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>FCD type IIB</td>
</tr>
<tr>
<td>22</td>
<td>24F</td>
<td>23</td>
<td>E</td>
<td>?FCD</td>
<td>R temporal,insula</td>
<td>SEEG</td>
<td>AMIRA</td>
<td>Y</td>
<td>Y</td>
<td>Nil</td>
<td>Cortical resection</td>
<td>1</td>
<td>HS</td>
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<td>SEEG</td>
<td>AMIRA</td>
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<td>AMIRA</td>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>L insula</td>
<td>SEEG</td>
<td>AMIRA</td>
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<td>EpiNav</td>
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<td>Y</td>
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<td>L centroparietal</td>
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<td>EpiNav</td>
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<td>FCD</td>
<td>L frontocentral</td>
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<td>EpiNav</td>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>Grids</td>
<td>EpiNav</td>
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<td>Grids</td>
<td>EpiNav</td>
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<td>Infection</td>
<td>Cortical resection</td>
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<td>EpiNav</td>
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<td>EpiNav</td>
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<td>Grids</td>
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<td>NA</td>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>22M</td>
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<td>L parietal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>DNET</td>
<td>R temporal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>Nil</td>
<td>Cortical resection</td>
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</tr>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>Y</td>
<td>Infection</td>
<td>Cortical resection</td>
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<td>R frontal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>EpiNav</td>
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<td>Surgical Procedure</td>
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<td>Grids</td>
<td>EpiNav</td>
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<td>EpiNav</td>
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<td>Excluded</td>
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<td>EpiNav</td>
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<td>34F</td>
<td>29</td>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>29M</td>
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<td>EpiNav</td>
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<td>29F</td>
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<td>bitemporal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>Y</td>
<td>Nil</td>
<td>Excluded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>31M</td>
<td>18</td>
<td>No</td>
<td>NA</td>
<td>L frontotemporal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>Excluded</td>
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<td>SEEG</td>
<td>EpiNav</td>
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<td>ND</td>
<td>NA</td>
<td>ND</td>
<td></td>
<td></td>
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<td>51</td>
<td>46F</td>
<td>41</td>
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<td>R temporal</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>NA</td>
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<tr>
<td>52</td>
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<td>LGG</td>
<td>R insula</td>
<td>SEEG</td>
<td>EpiNav</td>
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<td>NR</td>
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<td>Excluded</td>
<td>Cortical resection 1 LGG</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>29M</td>
<td>14</td>
<td>No</td>
<td>NA</td>
<td>L frontal</td>
<td>SEEG</td>
<td>EpiNav</td>
<td>N</td>
<td>ND</td>
<td>NA</td>
<td>Excluded</td>
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<tr>
<td>54</td>
<td>26M</td>
<td>25</td>
<td>No</td>
<td>NA</td>
<td>R frontal</td>
<td>SEEG</td>
<td>EpiNav</td>
<td>N</td>
<td>NR</td>
<td>Nil</td>
<td>Excluded</td>
<td></td>
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</tr>
</tbody>
</table>

Table 11-2 Demographics and Surgical Outcomes of study population
(F- female, M- male, FCD- focal cortical dyplasia, HS- hippocampal sclerosis, LGG- low grade glioma, DNET-dysembryoplastic neuroepithelial tumour, NA-not applicable, E-equivocal, L-left, R-right, EZ- epileptogenic zone, SEEG- stereo-electroencephalography, NR-not recorded, ND-not done, NAD-no abnormality detected)
The median age of the group was 32.5 years (range 19-60), and the median duration of epilepsy was 20.5 years (range 4-46). 37/54 (69%) patients were considered to have epilepsy that originated outside the temporal lobe, and 21/54 (39%) patients had no clear structural lesion.

All patients had a model of their cortex built, derived from cortical segmentations of a T1-weighted MRI generated by Freesurfer (Version 5.0.0, Martinos Centre for Biomedical Imaging, Massachusetts, USA). These cortical models provided the anatomical framework on which to add other modalities.

A further 253 imaging models were created and added onto these cortex models, resulting in a mean 5.7 models per patient (Figure 11-3). There were 82 models that helped to infer the EZ, 52 models of tractography and 69 models of venous/arterial vasculature. 4 patients undergoing grid implantations had pre-operative grid electrode models built. All 25 patients undergoing SEEG had models of individual electrode trajectories.

Figure 11-3 Imaging modalities used in case series
BLACK- cortex model derived from Freesurfer, BLUE- modalities to help localise the EZ, RED- modalities to help localise eloquent brain and critical structures, YELLOW- pre-operative electrode simulations. (Arc fasc- arcuate fasciculus, derived from tractography)
11.3.2 Disclosure of 3DMMI

54 patients were studied in this series, and the disclosure of 3DMMI changed some aspect of management in 43/54 (80%) cases. For each case, the change was in implantation strategy, precise surgical planning or both.

11.3.2.1 Implantation Strategy

44 patients entered the Implantation Strategy arm. See Figure 11-4 for an overview of the effect of 3DMMI on Implantation Strategy. The remaining 10 patients in the study were not included in this arm of evaluating the impact of 3DMMI on Implantation Strategy.

In 2 patients there was clinical equipoise as to whether an implantation was necessary or resection could be recommended without iEEG. With patient 21 this was due to the proximity of the presumed EZ to the motor cortex and corticospinal tract. Following disclosure of 3DMMI the team felt it was safe to proceed with resection. With patient 52 it was thought not possible to completely resect an extensive structural lesion. Disclosure of the models led the team to consider that an implantation was necessary to precisely localise the EZ and offer safe resective surgery.

42 patients were initially put forward for an intracranial implantation; 18 for grid implantations and 24 for SEEG implantations. Disclosure of the models led to a change in the implantation strategy in 13/42 (31%) cases. There were 5/18 (28%) changes in grid strategy and 8/24 (33%) changes in SEEG strategy.

The details of the 15 changes in implantation strategy are listed in the Table 11-3.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial strategy</th>
<th>Change in strategy</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Grids</td>
<td>Addition of depth electrodes</td>
<td>Improve coverage around lesion</td>
</tr>
<tr>
<td>20</td>
<td>Grids</td>
<td>Addition of depth electrodes</td>
<td>Improve coverage around lesion</td>
</tr>
<tr>
<td>21</td>
<td>Equipoise</td>
<td>Proceed to resection</td>
<td>Good spatial corroboration between lesion and SPECT, anterior to motor areas</td>
</tr>
<tr>
<td>22</td>
<td>SEEG</td>
<td>Addition of depth electrodes</td>
<td>Target MEG dipole in insula</td>
</tr>
<tr>
<td>24</td>
<td>SEEG</td>
<td>Removal of depth electrodes</td>
<td>Difficult implementation of SEEG</td>
</tr>
<tr>
<td>25</td>
<td>SEEG</td>
<td>Rediscussion in MDT</td>
<td>No initial consensus on agreed strategy.</td>
</tr>
<tr>
<td>27</td>
<td>SEEG</td>
<td>Addition of depth electrodes</td>
<td>Improve coverage around lesion</td>
</tr>
<tr>
<td>29</td>
<td>Grids</td>
<td>Displacement of grid</td>
<td>Include coverage of PET hypometabolism</td>
</tr>
<tr>
<td>31</td>
<td>SEEG</td>
<td>Grids</td>
<td>Anterior frontal MEG dipole, more amenable to grid coverage</td>
</tr>
<tr>
<td>32</td>
<td>Grids</td>
<td>Addition of depth electrodes</td>
<td>Improve coverage of tubers</td>
</tr>
<tr>
<td>34</td>
<td>SEEG</td>
<td>Removal of depth electrodes</td>
<td>Improve efficiency of implantation</td>
</tr>
<tr>
<td>36</td>
<td>Grids</td>
<td>Displacement of grid</td>
<td>Include coverage of PET hypometabolism</td>
</tr>
<tr>
<td>42</td>
<td>SEEG</td>
<td>Removal of depth electrode</td>
<td>Improve efficiency of implantation</td>
</tr>
<tr>
<td>47</td>
<td>SEEG</td>
<td>Addition of depth electrode</td>
<td>Improve coverage to map optic radiation</td>
</tr>
<tr>
<td>52</td>
<td>Equipoise</td>
<td>Proceed to SEEG</td>
<td>Further localise EZ in large low grade glioma</td>
</tr>
</tbody>
</table>

Table 11-3 Changes made in implantation strategy
(MDT-Multi-Disciplinary Team Meeting, SEEG-stereoelectroencephalography, SPECT-single photon emission computed tomography, MEG-magnetoencephalography, PET-positron emission tomography, EZ-epileptogenic zone)

11.3.2.2 Precise Surgical Planning
43 patients entered the Precise Surgical Planning arm. Of the 11 patients not included in this arm, 1 patient declined to proceed with an implantation, 1 patient proceeded direct to a resection, 4 patients have not had Precise Surgical Planning done and 5 patients did not
have their planning recorded. See Figure 11-4 for an overview of the effect of 3DMMI on surgical planning.

5 patients were planned for grid implantations only, 13 patients were planned for a combination of grid and depth electrode implantations, and 25 patients were planned for SEEG implantations.

Disclosure of the models did not change the planning in the 5 cases using a strategy of subdural grids without depth electrodes. Disclosure of the models changed 10/13 (77%) cases using a combination of grids and depth electrodes. Disclosure of the models changed 25/25 (100%) cases using a strategy of SEEG. 158/212 (75%) electrodes were changed, with 124 changes to entry points, 28 changes to target points, and the addition of 6 further electrodes by the surgeons to optimise coverage. The most common reasons for changes to entry points were to minimise the risk of a vascular injury, by increasing the distance from a cortical surface vein (51) or by centring on the crown of the gyrus (44). The most common reason for changes to target points was to sample structural lesions that were not seen on standard volumetric T1 weighted MRI (10). 6 electrodes were added to optimise coverage when the data was viewed as 3D models.

The details for the changes in SEEG implantation planning are listed in Table 11-4.
<table>
<thead>
<tr>
<th>Changes in electrode</th>
<th>Number</th>
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<td>Changes in entry point</td>
<td>124</td>
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<tr>
<td>Increase distance from vein</td>
<td>51</td>
</tr>
<tr>
<td>Centre on gyral crown</td>
<td>44</td>
</tr>
<tr>
<td>Improve feasibility of trajectory</td>
<td>14</td>
</tr>
<tr>
<td>Use of gyral anatomy</td>
<td>8</td>
</tr>
<tr>
<td>Centre on motor area (fMRI)</td>
<td>6</td>
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<tr>
<td>Avoid superficial temporal artery</td>
<td>1</td>
</tr>
<tr>
<td>Changes in target point</td>
<td>28</td>
</tr>
<tr>
<td>Target structural lesion</td>
<td>10</td>
</tr>
<tr>
<td>Increase distance from artery</td>
<td>8</td>
</tr>
<tr>
<td>Avoid electrode congestion</td>
<td>3</td>
</tr>
<tr>
<td>Improve feasibility of trajectory</td>
<td>3</td>
</tr>
<tr>
<td>Target PET/MEG</td>
<td>2</td>
</tr>
<tr>
<td>Target language areas (fMRI)</td>
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</tr>
<tr>
<td>Target motor areas (fMRI)</td>
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<tr>
<td>Added electrodes</td>
<td>6</td>
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<td><strong>Total</strong></td>
<td><strong>158</strong></td>
</tr>
</tbody>
</table>

*Table 11-4 Changes made in precise surgical planning of SEEG*
Figure 11-4 Overview of the effect of 3DMMI on implantation
A- An overview of the effect of 3DMMI on implantation strategy in this case series,
B- An overview of the effect of 3DMMI on precise surgical planning in this case series
(G&D- grids and depth electrodes)

11.3.3 Outcomes
In total 50 patients in this series underwent an ic-EEG (Table 11-2). 33/50 (66%) patients were put forward for a definitive cortical resection following identification of the presumed EZ, and 33 patients have had definitive cortical resections completed. 21/33 (64%) patients have ILAE Class I outcomes. Of the 17 patients excluded from surgery, the presumed EZ was found at multiple sites in 6 cases, diffuse in 5 cases, overlapped with eloquent cortex in
3 cases and was not clearly identified in 1 case. In the remaining 2 cases the patients did not have seizures and the implantations were abandoned after a given period of time.

11.4 Discussion

11.4.1 Summary

3DMMI was employed in the presurgical evaluation and surgical management of a consecutive series of patients with medically refractory epilepsy undergoing ic-EEG implantation. Of the 54 patients studied, the disclosure of 3DMMI changed some aspect of management in 43/54 (80%) cases, with a 34% rate of change in strategy, and 81% rate of change in planning. The total added value of 3DMMI can be expressed in our series as follows: 3 patients moved out of clinical equipoise into resective surgery, ic-EEG and rediscussion at the telemetry meeting respectively, 1 patient underwent a change in ic-EEG method, 11 patients underwent a fine-tuning of implantation strategy, and 35 patients underwent a change in precise surgical planning, comprising of changes to 3 grids and 173 depth electrodes in total. This suggests that 3DMMI has a role to play in evaluation and management.

The Implantation Strategy, that is the design of the general method for implantation, changed in 15/44 individuals. These changes were not generally from one technique to another, rather a fine tuning of implantation design. This includes the addition of electrodes to improve coverage of structural, functional and neurophysiological data, and the reduction of electrodes to minimise surgical risk and increase efficiency.

The choice of technique for implantation is dependent on a number of factors, including hypothesis for EZ, need for functional mapping, surgical risk and expertise of the treating team. In summary, patients with suspected seizure onset at the cortical surface, close to eloquent areas, will be more suited to subdural grid electrode implantation to facilitate extensive cortical mapping, whereas patients with suspected seizure onset at the depths of a
sulcus, or areas of cortex not accessible by grids, are more likely to benefit from SEEG. The strategy for implantation was therefore based largely on the neurophysiological hypothesis, which was arrived at prior to and independently of disclosure of 3DMMI. We would therefore not anticipate any substantial change in the chosen implantation technique with 3DMMI disclosure.

The results do however indicate how strategies can be improved upon when seen in the context of 3DMMI. This is in comparison to the previous convention in which some imaging is presented in 2D (ie structural MRI, FDG-PET), and some imaging is not presented at all (fMRI, DTI tractography). With implantation of subdural electrodes it is possible to accurately gauge sizing of the grids and strips to ensure spatial coverage of underlying structural and functional areas of interest. We found this particularly useful in ensuring adequate cortical coverage for the purposes of functional mapping of the motor cortex and language areas, and in covering areas of interest such as FDG-PET hypometabolism. With SEEG the 3D spatial arrangement of depth electrodes is very difficult to appreciate and communicate in 2D form. Adjustments can be made to ‘fill’ any obvious gaps in spatial coverage, and to remove electrodes that duplicate coverage and cause congestion. Furthermore, deep targeting of functional areas of interest is only possible with 3DMMI. We conclude that designing implantations is suboptimal without the ability to visualise the 3D spatial relationships between regions of interest and implanted contacts.

Precise surgical planning, that is the planning of the details of the implantation, changed in 35/43 cases.

Disclosure of 3DMMI did not change surgical planning in cases of grid implantation. Grid planning is essentially the determination of the sizing and positioning, which is completed in the Strategy phase. Neurosurgeons use 3DMMI to inform the correct placement of the grids, and the optimal placement of the overlying craniotomy but there is little discrete planning to record.
Disclosure of 3DMMI changed surgical planning in all 25 cases of SEEG. In total the majority of electrodes (158/212, 75%) were altered following disclosure of 3DMMI. This supports the notion that 3DMMI is helpful for the design and planning of SEEG. Entry points were changed primarily to reduce the risk of haemorrhagic complications associated with cortical vein injury, and to centre on the gyral crown to avoid encroaching pial boundaries. Other reasons for change included accurate targeting of superficial cortical structures such as motor cortex, and the facilitation of improved trajectory angles through the skull that were easier to implement. Target points were changed primarily to locate important structural and functional areas of interest, such as deep areas of FCD or FDG-PET hypometabolism.

After planning all of the individual electrodes, 3DMMI allowed the clinical team to review the assembled implantation, and identify defects in spatial coverage and areas of electrode congestion. In some cases this led to the addition of depth electrodes, or the further alteration in individual depth electrode trajectory.

In practice, surgical planning of SEEG is a complex process (Cardinale et al., 2013); in any electrode arrangement the entry and target point of a solitary electrode can impact on the entire arrangement, and it is not uncommon to make several changes following disclosure of 3DMMI. We concede that it is possible to plan in 2D and arrive at reasonable electrode configurations with safe trajectories. However, 3D representations of gyral anatomy and vasculature in particular allow the surgeon to make small changes to electrode positioning with a clear understanding of how this impacts proximity to other structures. We believe this is the crucial difference to planning in 2D, and makes for a more informed method that optimises safety considerations.

11.4.2 General

Throughout this study there has been a development in understanding how 3DMMI can be used to improve clinical care. In terms of modalities, structural and functional data appear most relevant in determination of strategy whereas vascular and gyral anatomy appear most
relevant in precise planning. However, disclosure of 3DMMI does not always represent a change in decision making, but rather an added tool to support and inform decision making. Feedback from the neurophysiology and neurosurgery teams suggests the following benefits of 3DMMI in clinical practice.

1. 3D spatial concordance between structural and functional localising investigations for EZ
2. 3D spatial relationship of presumed epileptogenic zone to surrounding critical structures
3. Avoidance of haemorrhagic complications in the planning and implementation of SEEG
4. Planning of grid placement for purposes of functional cortical mapping
5. Use of vessel segmentation and models of segmented gyral anatomy to provide navigational tool in craniotomy

With subdural grid implantations and subsequent cortical resections, 3DMMI can be used by the surgeon as an additional navigation tool. For example, models of cortical veins, allied with segmentations of complex gyral anatomy such as the central sulcus and pre- and post-central gyrus, can provide valuable corroboration tools to orientate the surgeon and to check neuronavigation registration accuracy. This becomes particularly powerful when the models are propagated as 2D models through the operating microscope during cortical resections (Gonzalez-Darder et al., 2010, Harput et al., 2014).

In addition to using 3DMMI in presurgical evaluation, we also used 3DMMI post-operatively to demonstrate the spatial positioning of electrode contacts. This involves the coregistration of post-operative CT to the pre-operative imaging, followed by surface extraction and thresholding to build 3D models of implanted electrodes. This provided a crucial tool in the understanding of implantation accuracy and outcome, and interpreting the generated
neurophysiological data. This is especially the case in those grid electrode implantations where it is not possible to directly visualise and photograph the cortical surface eg orbitofrontal cortex, and in depth electrodes targeting deep structures eg anterior hippocampus. There is the obvious limitation of brain shift (Nimsky et al., 2000), which is more pertinent to grid electrode implantations with associated large craniotomies, but can also occur in SEEG with the escape of CSF and effect of gravity on head position. For this reason, post-operative MRI is a valuable addition to directly show electrode positioning in an anatomical context (Yang et al., 2012); however, individual centres have to pass their own safety testing prior to acquisition of MRI with implantations in situ. In addition, there is the possibility of electrode contact shift during the recording period and after post op imaging, which may falsely localise the EZ on the cortical surface, although we did not encounter this in our series.

11.4.3 Implications
This study demonstrates the potential role of 3DMMI in clinical practice. We anticipate that 3DMMI will become increasingly important in the future, for several reasons. Ongoing research in advanced imaging techniques, such as voxel based analysis, EEG-fMRI and MEG will add further modalities to be considered in 3D anatomical space and presented to the clinical team. At the same time there is a trend towards less invasive and better tolerated investigations and treatments in neurosurgery, with much hope for neuroablative techniques such as SEEG-guided RF thermocoagulation, MRgLIT and MRgFUS therapy. A planning system that presents 3DMMI multimodal data and communicates with existing neuronavigation software will be essential in the delivery of future implantations and treatments.

11.4.4 Limitations
The aim of the current study was to describe how the use of 3DMMI can change clinical management. The study does not specifically address whether the changes in practice, as a
direct result of disclosure of the 3DMMI, make any substantial difference to the outcome of these patients. Whilst it is intuitive to think that more data will lead to better decision-making and therefore better outcomes, we do not have evidence for this.

Class I evidence for the use of 3DMMI in epilepsy surgery would require the design of a randomised controlled trial. This is problematic in clinical practice for the following reasons.

1) Epilepsy, even if restricted to refractory focal epilepsy, is an extremely heterogeneous condition with a heterogeneous population group

2) Epilepsy surgery is relatively uncommon, with low numbers

3) Assessing outcome after epilepsy surgery is complex

4) Use of models already partially integrated into the clinical pathway

An alternative approach is to examine secondary endpoints that are surrogate markers for outcome. Firstly, did the patients undergoing ic-EEG achieve a satisfactory conclusion to their implantation with regards to seizure localisation? 33/50 patients have been put forward for cortical resection and 17/50 patients have been excluded from resective surgery in this series. The EZ was satisfactorily identified in up to 42 of the 50 cases studied. This indicates that the final implantations were well designed. It will be some time before robust seizure outcome data is available in this patient group. At the present time 21/33 (64%) of patients have ILAE Class I outcomes at 1 year of follow up. These results are consistent with the literature when one considers the difficult patient group, with high rates of nonlesional and extratemporal epilepsy (De Tisi et al., 2011).

Secondly, did the patients undergoing IC-EEG suffer any complications as a result of IC-EEG implementation? There was 1 case of a haemorrhagic complication using a frameless stereotactic method for SEEG implantation out of a total of 212 electrodes implanted (0.5%). This patient was asymptomatic and did not require any further treatment. There was also one case of a superficial infection with SEEG at a wound site, which required a course of
antibiotics but no surgical intervention. With the grid cases there were 2 cases of subdural haematomas that required evacuation and precluded continued ic-EEG recording, and 3 cases of infection. This complication rate is comparable with the literature (Vale et al., 2013). Overall these events were not thought to be a result of the use of 3DMMI, and these surrogate markers are suggestive of good clinical practice.

A further caution is that the use of 3DMMI is dependent on the generation of high quality input data, which is well understood by the end user. We know that some data sets will be reliable and reproducible such as structural MRI, and other sets will have considerable inter-user variability such as tractography (Heiervang et al., 2006). Interpretation of these within an integrated data set requires differential levels of caution and confidence by the neurophysiologist and neurosurgeon. Taking the example of tractography we recommend incorporating distortion corrections and adding a safety margin prior to use, and using this as a guide to the orientation of large white matter tracts. Intra-operative mapping is required for definitive identification of white matter tracts. Similarly, the sensitivity of 3D phase contrast MRI is limited, and in our experience the segmentation of cortical veins derived from this modality is incomplete at the convexity of the hemispheres. It is therefore crucial for the surgeon to check the ‘probes eye view’ planes on the MRI with gadolinium, prior to implementing a trajectory planned with the vascular models.

The complexity of presurgical evaluation gives rise to two further limitations with this study. Firstly, there is the difficulty associated with capturing benefits. The terms ‘strategy’ and ‘planning’ are divisions made in a stepwise process. Presurgical evaluation extends over many months and often involves the exchange of ideas between the treating neurology and surgical team at multiple points along the course. In order to capture the impact of 3DMMI, a degree of rigidity was applied to this process, with the distinction of implantation strategy from precise surgical planning.
Secondly, there is difficulty capturing the entire workflow for a given number of patients. Since this study ran for 2 years, it represents a snapshot of the presurgical evaluation and surgical management in our unit. Although 54 patients passed through the study, only 44 were evaluated for strategy, 43 for precise surgical planning and 46 for outcome. The reasons for this are given above and reflected in the chronological order of Table 11-2; any attempt to homogenise the results to only patients passing through the entire process with 1 year follow-up would result in much data loss.

Finally the generalizability of our findings needs to be confirmed in other centres, which do not have the same degree of interest and expertise in 3DMMI. The EpiNav™ software is currently being made available to other units for this express purpose.

11.4.5 Further work

The next logical step to this work is to examine the utility of 3DMMI in planning definitive cortical resections. This is especially pertinent following SEEG implantations, where the EZ may be deep, difficult to access and without clear anatomical borders. In the present study for extratemporal resections, the surgeon has used the spatial positioning of implanted electrodes implicated in seizure origin, as well as aiming to remove the entirety of any segmented structural lesion present. In the future, we plan to generate resection models to guide surgery, that incorporate advanced imaging techniques and neurophysiological data, and that respect anatomical boundaries.
12 Comparison of computer-assisted and manual planning in the implantation of intracranial depth electrodes in epilepsy*

12.1 Introduction

SEEG planning is a necessary prerequisite to implementation. A number of factors are considered when planning an electrode arrangement for SEEG (Table 12-1). Individual electrodes should enter at the crown of the gyrus to avoid sulcal boundaries and should avoid vascular structures. Further, the electrode should enter at a reasonable angle to the perpendicular of the skull to enable the trajectory to be drilled with precision.

Current commercial planning solutions allow the user to select cerebral target and entry points, resulting in the generation of a planned trajectory. In the context of a multi-trajectory implantation, this individualised approach is time-consuming and inefficient, with a degree of trial and error necessary to avoid trajectory collision. There is no commercial product that offers computer assistance with planning, to improve either the safety profile or the efficiency of individual trajectories in SEEG.

The Milan group reported experience with an automated planner for use in SEEG, which maximises the distance of depth electrodes from blood vessels and avoids the sulci as cerebral entry points. This group reported individual depth electrode trajectories (De Momi et al., 2013), and multiple trajectories (De Momi et al., 2014), describing a quantitative and qualitative validation of the automated multi-trajectory planner with 26 electrodes in 3 patients. They concluded that automatic planners are clinically valuable for assisting SEEG planning, and potentially useful for brain biopsy and deep brain stimulation.

We have implemented a 3D multimodal brain imaging platform EpiNav™ (CMIC, UCL, London, UK), for epilepsy surgery planning (Nowell et al., 2014b, Nowell et al., 2015b) and
developed a multi-trajectory automated planner for SEEG. We have previously shown the principle of CAP in 6 patients, comprising of 52 electrodes, with lower risk values and more contact with grey matter. We have also demonstrated computational efficiency, with a median plan calculation time of 16.68 seconds for 9 trajectories (Sparks R, Zombori G, Vos S et al, Automated multiple trajectory planning algorithm for the placement of SEEG electrodes in epilepsy treatment. In submission, unpublished).

In this chapter we perform a comprehensive retrospective study with an emphasis on clinical validity, to compare the electrode trajectories in 18 patients who were planned manually, with trajectories determined using CAP.

<table>
<thead>
<tr>
<th>Individual electrode</th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avascular plane through brain</td>
<td>Reasonable entry point on scalp</td>
<td></td>
</tr>
<tr>
<td>Accurately hit target</td>
<td>Less than 30 degrees angle of traverse of skull</td>
<td></td>
</tr>
<tr>
<td>Avoid deep sulci at the cortical surface</td>
<td>Over 3mm safety margin to critical structures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximise number of contacts in grey matter</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrode arrangement</th>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good 3D spatial sampling</td>
<td>Avoid redundant coverage</td>
<td></td>
</tr>
<tr>
<td>Avoid electrode collision</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 12-1 Requirements of individual and multiple depth electrodes*

12.2 Method

12.2.1 Demographics

All individuals with medically refractory focal epilepsy, undergoing planning for SEEG between August 2013 and August 2014, were invited to participate in the study and provided
informed consent. This represents a subset of the patient group described in the previous study.

12.2.2 Data preparation

Patients undergoing planning for SEEG underwent volumetric gadolinium-enhanced T1 weighted MRI (Siemens Avanto 1.5T, field of view 512x512x144, voxel size 0.5x0.5x1.5mm³), and dedicated vascular imaging in the form of 3D phase contrast MRI (Siemens Avanto 1.5T, field of view 256x256x160, voxel size 0.85x0.85x1mm³) and CTA (Siemens Somatom Definition AS, field of view 512x512x383, voxel size 0.43x0.43.0.75 mm³) in patients in whom high risk peri-sylvian trajectories were anticipated.

Image integration and visualisation was performed on EpiNav™ (CMIC, UCL, London, UK). The T1 weighted MRI image was the reference image, upon which other modalities were coregistered. CTA and 3D phase contrast images were processed using vessel extraction software available on EpiNav™ (CMIC, UCL, London, UK) (Zuluaga et al., 2014). Grey matter, surface sulcal and cortical segmentations were derived from T1 weighted MRI using Freesurfer software (Version 5.0.0, Martinos Centre for Biomedical Imaging, Massachusetts, USA). Scalp exclusion masks were generated based on the T1 weighted MRI using basic imaging tools in EpiNav™ and MeshLab (Version 1.3.3, University of Pisa, Italy). All models were stored and used as surface renderings (Figure 12-1).
Figure 12-1 Data preparation from computer-assisted planning
Stages include image acquisition, coregistration followed by 3D surface rendering

12.2.3 Software


EpiNav™ is a dedicated platform for image integration, 3D visualisation and surgical planning in epilepsy surgery. The automated multi-trajectory planner calculates optimised electrode configurations in real time, based primarily on reduced cumulative risk scores and within a set of pre-determined constraints. The workflow for CAP is given below:

1. Target points set by user
2. Trajectories identified that meet the user-defined constraints of electrode length and angle traversing the skull

3. Trajectories selected where entry points are limited to an individually tailored scalp exclusion mask, which excludes anatomical areas not appropriate for electrode entry such as the face

4. Primary sort of trajectories that optimise the distance from ‘critical structures’, defined as models of surface sulci and cerebral vasculature

5. Secondary sort of trajectories to optimise the proportion of electrode in grey matter, within an accepted risk profile

Following planning of electrode trajectories, the user can examine the electrode trajectory, scrolling along the length of the electrode with a ‘Probe’s Eye viewer’, inspecting the minimum distance to the closest defined critical structure, as well as the proximity of grey matter.

For each trajectory a number of metrics are presented (Figure 12-2).

- Electrode length: length of the trajectory from the scalp entry point to the cerebral target point
- Angle: angle of entry at the skull, where 0 degrees represents the perpendicular.
- Risk: the cumulative risk across the length of the electrode. This is calculated by taking the area that the electrode resides in the ‘risk zone’, which is defined as lying between 3 and 10mm to the nearest blood vessel from point of cortical entry to target. An electrode that never passes within 10mm of a blood vessel is given the average risk value 0. An electrode that passes to within 3mm is automatically given an average risk value of 1. This is a somewhat arbitrary value, but is required to drive the CAP to optimise electrode safety.
- Minimum distance: lowest distance along the length of the trajectory to the nearest blood vessel, expressed in mm. This is a less arbitrary value that is easily understood by clinicians.

- Grey-white matter (G/W) ratio: defined as the proportion of the electrode from the cortical surface to the cerebral target point that lies within grey matter. This is a reflection of the efficacy profile of the electrode, since recordings from grey matter are of greater utility than recordings from white matter when determining the source of epileptic activity.

Figure 12-2 Graphic visualisation of metrics associated with individual trajectories
Top- length, angle traversing skull, risk, G/W ratio and minimum distance from a blood vessel>1mm in diameter.
Middle- graphic display of closest critical structure along length of trajectory (red-artery, cyan-venin, y-axis- distance to structure(maximum 10mm), x-axis- distance along trajectory from brain entry to target, SM- safety margin represented as horizontal red line that marks 3mm separation of trajectory to critical structure).
Bottom- graphic display of trajectory path through grey and white matter (green-extracerebral, grey-grey matter, white- white matter).

12.2.4 Manual planning
Previously each case had been discussed at a Multi-Disciplinary Team Meeting, involving Neurologists, Neurophysiologists, Neuroradiologists, Neuropsychologist, Psychiatrists, and Neurosurgeons. Targets for depth electrode coverage were agreed, and manual planning of the implantation had taken place on EpiNav™ using conventional techniques for individual electrodes. These manual plans were stored on a single workstation, following implementation in the operating theatre. With the development of CAP the manual plans
were re-examined, extracting the quantitative metrics of electrode length, angle of entry, risk, minimum distance and grey-white matter ratio.

12.2.5 CAP

The 3D target coordinates were re-entered into a New Plan, and CAP on EpiNav™ was run to derive a new automated plan, with new associated metrics for individual electrodes. The initial user constraints used were electrode length 80mm and entry angle within 15 degrees of perpendicular to the skull, with a minimum distance of 1cm between trajectories. These constraints were selected to generate trajectories with short intracerebral lengths that would be straightforward to drill and implement in theatre. Suitable individual trajectories were ‘locked’, and CAP was rerun with adjusted user constraints for the remaining electrodes. In this way, an electrode configuration was generated that could accommodate differential requirements for individual electrodes.

12.2.6 Feasibility of implementation

All manual planning is feasible, as these plans had already been implemented in clinical practice.

The feasibility of implementation of the results of CAP was assessed by 3 epilepsy neurosurgeons independently using the EpiNav™ software. Each electrode trajectory was examined for scalp and cortical entry points using 3D computer models, and avascular paths were checked using the Probe’s Eye viewer. The trajectory was then given a pass or fail in terms of feasibility of clinical implementation. If 2/3 neurosurgeons ‘passed’ a trajectory it was deemed to be clinically feasible.

In addition, the neurosurgeon was presented with the overall electrode arrangement derived from manual planning and CAP in a blinded way, and was asked to determine feasibilities of entire implantations (figure 12-3).
One of the three neurosurgeons was involved in both manual planning and CAP. However, CAP was 3-15 months after the prior manual planning, reducing the risk of bias in the study.

Figure 12.3 3D visualisation of manual (blue) and computer-assisted (purple) planning
A—scalp (white), scalp exclusion mask (yellow), B—brain added (pink), C—scalp and mask removed, and veins (cyan) added, D) brain removed and arteries (red) and surface sulci (green) added

12.3 Results

18 patient implantations were studied, comprising 166 electrodes, with a range of 6-12 per patient. Demographics of the patient group are described in Table 12-2.
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/Sex</th>
<th>Presumed EZ</th>
<th>Number of electrodes</th>
<th>Vascular models</th>
<th>Duration of CAP (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29M</td>
<td>L frontal</td>
<td>13</td>
<td>Veins</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>29M</td>
<td>L frontal</td>
<td>10</td>
<td>Veins, Arteries</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>19F</td>
<td>R occipital</td>
<td>9</td>
<td>Veins, Arteries</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>27M</td>
<td>R parietal</td>
<td>10</td>
<td>Veins</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>40M</td>
<td>R occipital</td>
<td>11</td>
<td>Veins, Arteries</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>32M</td>
<td>R temporal</td>
<td>7</td>
<td>Veins, Arteries</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>19M</td>
<td>R frontal</td>
<td>7</td>
<td>Veins, Arteries</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>37F</td>
<td>R temporal</td>
<td>7</td>
<td>Veins</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>29M</td>
<td>R temporal</td>
<td>12</td>
<td>Veins</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>31M</td>
<td>L frontal</td>
<td>11</td>
<td>Veins, Arteries</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>42F</td>
<td>R frontal</td>
<td>8</td>
<td>Veins, Arteries</td>
<td>13</td>
</tr>
<tr>
<td>12</td>
<td>22F</td>
<td>R parietal</td>
<td>8</td>
<td>Veins</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>37M</td>
<td>R insula</td>
<td>11</td>
<td>Veins, Arteries</td>
<td>6</td>
</tr>
<tr>
<td>14</td>
<td>32F</td>
<td>L temporal</td>
<td>7</td>
<td>Veins</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>26M</td>
<td>R frontal</td>
<td>8</td>
<td>Veins, Arteries</td>
<td>4</td>
</tr>
<tr>
<td>16</td>
<td>44M</td>
<td>R frontal</td>
<td>7</td>
<td>Veins, Arteries</td>
<td>7</td>
</tr>
<tr>
<td>17</td>
<td>61F</td>
<td>R temporal</td>
<td>8</td>
<td>Veins, Arteries</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>42M</td>
<td>R temporal</td>
<td>12</td>
<td>Veins, Arteries</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 12-2 Demographics of the patient study group and time taken for computer-assisted planning

All manual planning had previously been implemented in clinical practice. In 11/18 patients a putative EZ was identified following SEEG that was amenable to resection, and these patients proceeded to resective surgery. In 4/18 patients, the putative EZ was identified, but cortical resection was not proceeded with due to the risk of neurological deficit. The
implantation failed to localise the EZ in 2 patients, and was prematurely terminated in one patient on request before an adequate duration of recording. There was 1 haemorrhagic complication, which occurred on removal of electrodes. This resulted in a mild temporary upper limb weakness, and did not require any surgical intervention.

CAP generated 163/166 (98.2%) trajectories. There were 3 cerebral targets for which no trajectory was found that satisfied the user constraints. These included two orbitofrontal targets and one anterior hippocampal target.

12.3.1 Metrics
A comparison of the results of manual planning versus CAP is demonstrated in table 12-3 and figure 12-4. We assessed the differences accounting for the correlation induced by the repeated measurements for each patient, using multilevel models with a varying (patient-specific) intercept.

Manual planning resulted in a median electrode length of 57.9 mm (interquartile range (IQR) 21.8) and a median angle of traversing the skull of 16.2 degrees (IQR 12.9) off the perpendicular. CAP resulted in a median electrode length of 53.9mm (IQR 15.6) and a median angle of traversing the skull of 13.0 degrees (IQR 7.6) off the perpendicular. These differences are likely to be due to the angle of entry being a constraining factor in CAP, generating more perpendicular and consequently shorter electrode lengths.

Manual planning resulted in a median risk value of 0.41 (IQR 0.79), with a median minimum distance to a critical structure of 4.48mm (IQR 2.99) and a median grey-white matter ratio of 0.33 (IQR 0.33). CAP results in a median risk value of 0.36 (IQR 0.43), with a median minimum distance to a critical structure of 4.52mm (IQR 2.97) and a median grey-white matter ratio of 0.48 (IQR 0.27).

Applying standard regression models with random effect, there is significant difference between Manual Planning and CAP in terms of all metrics measured (Table 12-3). CAP
generates shorter trajectories, that traverse the skull closer to the perpendicular, with lower risk values, greater minimum distances to critical structures and higher grey-white matter ratios.

CAP was better at avoiding high risk trajectories, defined as those that pass within 3mm of a critical structure, giving a risk value of 1 or above. This occurred in 44 trajectories with manual planning, and in only 9 cases in CAP.

<table>
<thead>
<tr>
<th></th>
<th>Manual planning*</th>
<th>CAP*</th>
<th>Estimated difference (Manual-CAP)</th>
<th>Error</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrode length (mm, 1dp)</strong></td>
<td>57.9 (21.8)</td>
<td>53.9 (15.6)</td>
<td>4.74</td>
<td>1.59</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Angle of entry (degrees off perpendicular, 1dp)</strong></td>
<td>16.2 (12.8)</td>
<td>13.0 (7.6)</td>
<td>5.89</td>
<td>1.07</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Risk (normalised units, 2dp)</strong></td>
<td>0.41 (0.79)</td>
<td>0.36 (0.42)</td>
<td>0.19</td>
<td>0.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Minimum distance from blood vessel (mm, 1dp)</strong></td>
<td>4.5 (3.0)</td>
<td>4.5 (3.0)</td>
<td>-0.56</td>
<td>0.20</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Proportion of intracerebral electrode in grey matter (2dp)</strong></td>
<td>0.33 (0.33)</td>
<td>0.48 (0.28)</td>
<td>-0.11</td>
<td>0.02</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*first value is median, second value in brackets is IQR
### Table 12-4 Causes for computer-assisted planning electrode trajectories that required manual adjustment

<table>
<thead>
<tr>
<th>Reason for classification of failed trajectory</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximity to blood vessel (missing from 3D vessel model)</td>
<td>18</td>
</tr>
<tr>
<td>Proximity to blood vessel (included in 3D vessel model)</td>
<td>5</td>
</tr>
<tr>
<td>Proximity to superior sagittal sinus</td>
<td>6</td>
</tr>
<tr>
<td>Proximity to deep sulcus</td>
<td>4</td>
</tr>
<tr>
<td>Entry point not feasible</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35</strong></td>
</tr>
</tbody>
</table>

Figure 12-4 Comparison of manual planning versus computer-assisted planning
A) electrode length, B) angle of entry, C) risk and D) grey-white matter ratio.
In each graph the x-axis represents manual planning and the y-axis represents computer-assisted planning. Each point represents the value of the given metric for manual and computer-assisted planning. Any point located below the diagonal line means that the value derived from manual planning is greater than that from computer-assisted planning and vice versa. For A, B and C, values below the line indicate superiority of CAP over manual planning. For D values above the line indicate superiority of CAP over manual planning.

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12.3.2 Feasibility

131/166 (78.9%) of individual CAP trajectories were deemed suitable for clinical implementation without adjustment, in terms of appropriate scalp and cortical entry points and avascular paths, following independent review by 3 neurosurgeons. 35 trajectories required manual adjustment, most commonly because of proximity to blood vessels that were evident on the Probe's eye view projection but not represented as a surface rendered structures due to suboptimal segmentation. Work is ongoing to improve the quality of vessel segmentation.

18/18 (100%) implantations planned using CAP were deemed to be feasible for clinical implementation.

12.3.3 Timing

The prior manual SEEG planning typically took 2-3 hours per patient, although the duration was not prospectively recorded, and we recognise this is as a limitation to our study. The duration of the computer-assisted planning is recorded in table 12-2. The median duration of computer-assisted planning was 8 minutes. This includes the generation of the trajectories as well as the checking of the trajectories with the 3D models, the risk visualisation graph and the probes eye viewer in a comprehensive and detailed manner. Duration was largely dependent on the number of ‘rounds’ of CAP that were needed to satisfy individual trajectory constraints. However, this does not take into account the time taken for data preparation (generation of scalp exclusion mask and models of sulci and grey matter), which can take 20-30 minutes in total per patient. Additionally, this does not take into account the time taken for the manual adjustment of trajectories that were not considered feasible, which takes approximately 2-3 minutes per electrode.
12.4 Discussion

12.4.1 Summary
The process of manual planning in SEEG is time consuming and complex, with the dual aims of achieving good coverage of the putative EZ and network, and adjacent eloquent cortex, and ensuring safe, practical trajectories. In the previous chapter we demonstrated that planning is assisted by the use of 3D multimodality imaging, demonstrating the spatial relationships between planned trajectories, structural and functional regions of interest, gyral anatomy and cortical vasculature (Rodionov et al., 2013, Nowell et al., 2015b).

We describe CAP, which has been tested on 18 historical cases comprising 166 depth electrodes. CAP provides rapid, optimised solutions for electrode configurations, with statistically significant improvements in risk value and grey/white matter capture compared with conventional manual planning, and with substantial savings in time within the framework of a 3D multimodality model.

The purpose of CAP in this study was to find alternate trajectories for defined electrodes. There is no current functionality that aims to reduce the number of electrodes required for coverage, although this is an exciting area for future work.

12.4.2 Data preparation
For CAP to be effective, good data preparation is paramount. Individually tailored scalp exclusion masks are needed to avoid inappropriate skull entry points on the face, ears, below the tentorium cerebelli and crossing the midline. The use of surface sulcal models is important to centre the electrodes on the crown of the gyri, although it is acknowledged that some surgical groups accept crossing sulcal boundaries. Most importantly, the quality of the risk values is dependent on quality of the segmentations of vascular structures. In this series the most common reason for trajectories being rejected for clinical implementation was proximity to blood vessels that were not included in the surface models. Complete vessel
segmentation is difficult to achieve without invasive cerebral angiography, which adds considerably to the patient workup and pre-operative risk. Our group continue to work on this problem, with possible roles for centre lining vessel structures, derived from multiple sources of non-invasive vascular imaging, and dual energy CT angiography.

Data preparation takes time. In our experience, complete 3D multimodality image integration for any patient using EpiNav™ takes 20-30 minutes, and this does not take into account the post-processing done using third party software. In our centre it is routine for all patients undergoing an ic-EEG study to have 3D multimodality image integration performed, as we have previously demonstrated clinical utility in decision making (Nowell et al., 2015b). We would therefore not consider data preparation as an additional step in our own workflow, although this may not be true in other centres and should be factored in to any proposed time savings.

12.4.3 Risk reduction

In this series, the reduction of risk from CAP is reflected in the reduced risk value. It is important to acknowledge that this value is representative of cumulative risk over the length of the electrode. As an absolute value, this is of limited use to the clinician, as it is heavily affected by the critical structures presented. Risk cannot be compared across different patients, since the quality of image acquisition and segmentation varies. However, the value is most useful for comparing CAP with manual planning in a single patient with the same critical structures segmentation. In contrast, ‘least distance to the nearest critical structure’ is an easy metric to understand. In this series there was a significant increase in this metric when using CAP, giving further evidence that CAP improves the safety profile of implantations. However, the translation of this metric into actual reduction in haemorrhage rate is difficult to demonstrate in this small series.

12.4.4 Increasing grey matter capture- making electrodes work harder
With manual planning the median proportion of trajectories in grey matter was 0.33, compared with 0.48 in CAP. It is intuitive that increasing the proportion of electrodes in grey matter improves the chances of siting individual contacts in grey matter, with a corresponding improvement in the 3D capture of epileptic activity and neurophysiological ‘yield’, although this has not been demonstrated in this study.

The next step to improve efficacy is to model electrode contacts in the planning stage, with the aim of siting these in grey matter segmentations. This would reduce the ‘waste’ of redundant contacts that lie in white matter. An alternative approach would be to plan electrode implantations, and subsequently custom design individual electrodes with contact spacing to optimise grey matter contacts. For either to be effective, a very precise method of SEEG implementation will be required, with 1-2mm target point precision.

12.4.5 Feasibility

The feasibility study performed by 3 neurosurgeons on the CAP implantations demonstrated two findings.

Firstly, individual electrodes trajectories generated with CAP were generally felt to be safe and feasible for clinical implementation. A small proportion of trajectories had to be revised on account of failures of vessel segmentation, and a small number of trajectories were rejected because of proximity to segmented vessels and deep sulci. This reinforces the caveat that all trajectories need to be thoroughly cross-checked using Probe’s eye view with conventional imaging before they are accepted for clinical implementation.

Secondly, the overall trajectory configurations generated were also feasible for clinical implementation. A given constraint to CAP is that trajectories are spaced by at least 1cm. However, at present there is no functionality in EpiNav™ to space the trajectories in a more even fashion on the cortical surface. Further, there is no weighting of the vascular surface renderings, with a consequence that CAP makes no distinction between large vascular
structures (ie the superior sagittal sinus) and smaller surface veins. This could be addressed in the future by generating a more limited scalp exclusion mask that excludes a longitudinal strip along the midline.

Perhaps the strongest limitation to this feasibility study is that it only examines how to safely design trajectories to a target point, with little emphasis on the importance of the cortical entry point and traversing grey matter. Since the entire length of the trajectory is important to the capture of epileptic activity, it is possible that the CAP configurations are less effective at capturing desired superficial cortical EEG activity. Also, some surgeons choose to implant electrodes along specific trajectories, for example a longitudinal placement of hippocampal electrodes with an occipital entry point (Bekelis et al., 2013) Although this introduces surgical bias into the CAP, it is likely to be required for optimisation. These limitations will be resolved by further constraining the target entry zones of specific electrodes, making CAP trajectories not just feasible but optimal for delineating the EZ.

A cortical parcellation library of the patient’s individual brain would facilitate the design of efficient electrode trajectories that sample both superficial convexity cortex and deep targets that are of interest, and would also allow for differential electrode constraints in a single ‘application’ of CAP. For example, an entry point in left anterior superior frontal gyrus and a target in the anterior left insula, which would present a very constrained number of possible trajectories, and would be more efficient computationally. This would also give the user more control in designing an evenly spaced trajectory configuration that does not run close to large vascular structures. Our group is currently working towards incorporating this into our version of CAP.

12.4.6 Clinical utility

A pertinent question raised by this study is whether the gains that are described translate to true clinical utility in actual practice, in terms of fewer complications and better determination of the EZ. Randomised controlled trials are notoriously difficult to perform in epilepsy surgery
due to the heterogeneity of the patient group. Our group plan to incorporate CAP into a prospective SEEG planning study, with the addition of a cortical parcellation library and more complete vascular segmentations, where the surgeon uses CAP as a starting point to the planning process, prior to manual checking and adjustment.

In the future it is possible that CAP may establish certain ‘corridors’ for defined trajectories, based on feasibility studies and these metrics of safety and risk. It is attractive to then consider a ‘menu’ of trajectory implantations that are selected ‘off the shelf’ and that undergo minor adjustments tailored to that individual patient’s anatomy. This would have the benefits of safety, efficiency and time-saving, as well as standardising SEEG implantation across different centres, making for easier clinical and research collaboration.

12.5 Conclusions

CAP is a promising tool to plan SEEG implantations. CAP provides feasible depth electrode arrangements, with quantitatively greater safety and efficacy profiles, and with substantial savings in duration of planning.

Further, CAP has possible uses beyond SEEG, in the planning of the insertion of any hardware into the brain. As minimally invasive treatments become more popular in neurosurgery, safe planning tools that increase safety and efficacy will become increasingly important (Nowell et al., 2014a).
13 A novel method for implementation of frameless stereoEEG in epilepsy surgery*

13.1 Introduction

SEEG implementation is a well-established frame-based technique (Talairach et al., 1962, Talairach and Szikla, 1980, Talairach and Tournoux, 1988). The advantage of frame-based techniques is the accuracy of electrode delivery to a predefined target, with a quoted median target point localisation error of 2.02 mm, IQR of 1.37-2.96 mm, and major complication rate of 2.4% (Cardinale et al., 2013). However there are several disadvantages that include potential patient discomfort, additional time for frame placement, restricted access to the surgical field and a limited ability to define new trajectories in real time during surgery. Additionally there are the costs associated with specialist equipment, the need for additional intra-operative imaging and training in frame-based techniques.

In this chapter we describe our technique and experience in the implementation of frameless SEEG in a single centre.

13.2 Method

13.2.1 Preparation

Patients underwent routine presurgical evaluation for epilepsy surgery at the NHNN, and individuals needing SEEG were selected on a case by case basis following a multi-disciplinary team meeting and subsequent focused strategy meeting led by neurophysiologists. These patients underwent pre-operative navigation T1-weighted volumetric MRI with gadolinium enhancement, 3D phase contrast MRI for visualisation of veins and CT angiography for visualisation of arteries.
Image integration was performed on the EpiNav™ software system (Centre of Medical Imaging and Computing (CMIC), University College London (UCL), UK), and any relevant additional functional and structural imaging performed during evaluation was incorporated.

Pre-operative surgical planning of electrodes with 3D multimodal integration was performed by the Epilepsy surgery team, including two neurosurgeons on the EpiNav™ (CMIC, UCL, UK) software system. The planned arrangement was then exported to an S7 StealthStation in the operating theatre. Each planned trajectory was checked by two neurosurgeons on the StealthStation prior to implementation.

Patients were consented for frameless stereoEEG. Frame-based implantation was not offered to patients in our unit, due to surgeons’ preference, but was described as an alternative technique that can be performed elsewhere, that carries a higher accuracy rate.

13.2.2 Surgery
Patients underwent a scalp fiducial marker registration (Pfisterer et al., 2008). The crucial steps of SEEG implementation comprised.

- Apply SureTrack tool to Guide Frame DT, and register to S7 StealthStation
- Select a planned trajectory on the StealthStation
- Mark entry point on the scalp for electrode entry and perform stab incision
- Line up manually the Guide Frame DT, loaded on the Medtonic arm, using the Guidance View option
- Lock trajectory, and use a system of custom designed reducing tubes to perform the following steps through the Guide Frame DT with real time neuronavigational feedback:
  - Create a hammered divot in the outer table of the skull using a custom designed spike (Adtech, Medical Instrument Corporation)
  - Drill through skull and perforate dura
• Screw in electrode bolts (Adtech, Medical Instrument Corporation, outer diameter 1.9-2.5 mm, length 21 mm)

• Using Stealth Probe, reset the entry point of the planned trajectory to the tip of the electrode bolt to calculate the updated length of electrode

• Use a rigid extraventricular drain stylette (8F Silverline, Spiegelberg) to ensure dural opening and create the intraparenchymal trajectory for the electrode, minimising subsequent electrode deviation. Stylette set to correct intracranial length using plastic stopper

• Insert electrode to appropriate length and secure with screw top. (Adtech, Medical Instrument Corporation, Spencer depth electrodes, range from 4, 6, 8 and 10 contacts)

See figures 13-1 and 13-2.

Figure 13-1 Equipment used in frameless SEEG
A) DT guide frame device, B) DT guide frame device with SureTrack device attached C) DT guide frame and SureTrack device with metal spike inserted, D) Delivery of hammered pivot into outer table of skull under frameless stereotactic conditions E) Drilling of trajectory under frameless stereotactic conditions

Figure 13-2 Post-operative appearance of bolts and electrodes
A) Percutaneous electrode bolts, B) Electrodes secured within percutaneous bolts
A post-operative CT head is performed 4 hours after surgery to check the placement of the electrodes and exclude an intracranial haemorrhage. The patient is then transferred to the telemetry ward for ic-EEG recording.

13.2.3 Accuracy

Accuracy of electrode placement is assessed in two ways:

13.2.3.1 Qualitative assessment
The post-operative CT is coregistered with the presurgical 3D multimodal models using AMIRA software (Visualisation Sciences Group, FEI), and the individual electrodes are segmented as 3D models. The position of the electrodes relative to the cortical and subcortical structures is examined by the neurophysiologist, in association with the neurophysiological findings. A dichotomous assessment is made on whether the electrodes are reaching their designated targets or not. See figure 13-3.

![Figure 13-3 Post-operative reconstructions of brain and SEEG electrode placements](image)

**Figure 13-3** Post-operative reconstructions of brain and SEEG electrode placements
A) Left anterior hippocampal electrode, indicated by red square. B) Coronal cross section showing hippocampal electrode at depth

13.2.3.2 Quantitative assessment
The post-operative CT is uploaded onto the S7 StealthStation, and coregistered with the patient’s pre-operative imaging using the StealthMerge tool as part of the S7 software. The electrodes are segmented out as 3D models, and for each electrode model a new implemented trajectory is created passing directly through the bolt trajectory. A quantitative comparison is then performed between the planned trajectory, implemented trajectory and actual electrode placement. See figures 13-4 and 13-5. This gives measures of the accuracy of trajectory delivery (TA), the degree of intraparenchymal electrode deviation (ED) and a final assessment of the accuracy of electrode delivery (EA), which corresponds to the lateral perpendicular shift at the planned target point.
Figure 13-4 Schematic representation of quantitative measures used in this study (a) trajectory accuracy, lateral shift between planned and executed trajectories, in plane perpendicular to executed trajectory that passes through target point (TA), (b) electrode deviation, lateral shift between electrode contact and executed trajectory, in plane perpendicular to executed trajectory that passes through target point (ED), (c) electrode accuracy, lateral shift between electrode contact and planned trajectory, in plane perpendicular to planned trajectory at target point (EA), (d) deviation of electrode length from planned trajectory, as seen in trajectory view on S7 StealthStation (L)
Figure 13-5 Workflow for calculating trajectory accuracy (TA), electrode deviation (ED) and electrode accuracy (EA)

A- 3D model of selected electrode, derived from post-operative CT and loaded on S7. Yellow – electrode reconstruction, blue – planned trajectory, orange – executed trajectory through electrode bolt.

B- Trajectory accuracy (TA); lateral shift between planned and executed trajectories, in plane perpendicular to executed trajectory that passes through target point.

C- Electrode deviation (ED); lateral shift between electrode contact and executed trajectory, in plane perpendicular to executed trajectory that passes through target point.

D- Electrode accuracy (EA); lateral shift between electrode contact and planned trajectory, in plane perpendicular to planned trajectory at target point.

13.3 Results

13.3.1 Demographics

22 patients were included in this case series. The demographics are shown in table 13-1. There were 9 non lesional cases and 13 lesional cases. There were 7 temporal cases, with 2 bitemporal cases, and there were 13 extratemporal cases. The median time for implantation was 137 minutes, with a range of 80-167 minutes.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Years since diagnosis</th>
<th>Lesional</th>
<th>Description</th>
<th>Presumed EZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41M</td>
<td>16</td>
<td>Yes</td>
<td>Grey matter heterotopia/HS</td>
<td>Right temporal</td>
</tr>
<tr>
<td>2</td>
<td>24F</td>
<td>23</td>
<td>Equivocal</td>
<td>FCD</td>
<td>Left parietal</td>
</tr>
<tr>
<td>3</td>
<td>52M</td>
<td>19</td>
<td>Yes</td>
<td>HS</td>
<td>Left frontotemporal</td>
</tr>
<tr>
<td>4</td>
<td>22M</td>
<td>21</td>
<td>No</td>
<td>NA</td>
<td>Left posterior quadrant</td>
</tr>
<tr>
<td>5</td>
<td>40M</td>
<td>34</td>
<td>No</td>
<td>NA</td>
<td>Left temporocentroparietal</td>
</tr>
<tr>
<td>6</td>
<td>41M</td>
<td>31</td>
<td>Yes</td>
<td>Encephalomalacia</td>
<td>Left frontocentral</td>
</tr>
<tr>
<td>7</td>
<td>55F</td>
<td>20</td>
<td>No</td>
<td>NA</td>
<td>Bitemporal</td>
</tr>
<tr>
<td>8</td>
<td>29M</td>
<td>11</td>
<td>Yes</td>
<td>Encephalomalacia</td>
<td>Left frontocentral</td>
</tr>
<tr>
<td>9</td>
<td>18M</td>
<td>7</td>
<td>Equivocal</td>
<td>FCD</td>
<td>Right temporal</td>
</tr>
<tr>
<td>10</td>
<td>19F</td>
<td>10</td>
<td>Yes</td>
<td>Low grade glioma</td>
<td>Right occipital</td>
</tr>
<tr>
<td>11</td>
<td>27M</td>
<td>17</td>
<td>No</td>
<td>NA</td>
<td>Right parieto-occipital</td>
</tr>
<tr>
<td>12</td>
<td>40M</td>
<td>35</td>
<td>No</td>
<td>NA</td>
<td>Right occipital</td>
</tr>
<tr>
<td>13</td>
<td>22M</td>
<td>11</td>
<td>Yes</td>
<td>Encephalomalacia</td>
<td>Left posterior quadrant</td>
</tr>
<tr>
<td>14</td>
<td>32M</td>
<td>15</td>
<td>Yes</td>
<td>Low grade tumour</td>
<td>Right temporal</td>
</tr>
<tr>
<td>15</td>
<td>37F</td>
<td>17</td>
<td>Yes</td>
<td>Low grade tumour</td>
<td>Right posterior quadrant</td>
</tr>
<tr>
<td>16</td>
<td>19M</td>
<td>14</td>
<td>No</td>
<td>NA</td>
<td>Right frontal</td>
</tr>
<tr>
<td>17</td>
<td>44M</td>
<td>38</td>
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</tr>
<tr>
<td>18</td>
<td>34F</td>
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<td>Yes</td>
<td>Frontal atrophy</td>
<td>Left temporal</td>
</tr>
<tr>
<td>19</td>
<td>29F</td>
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<td>Yes</td>
<td>FCD</td>
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</tr>
<tr>
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<td>42F</td>
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<td>NA</td>
<td>Right frontocentral</td>
</tr>
<tr>
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<td>22F</td>
<td>16</td>
<td>No</td>
<td>NA</td>
<td>Right temporal</td>
</tr>
<tr>
<td>22</td>
<td>29M</td>
<td>21</td>
<td>Yes</td>
<td>Schizencephaly</td>
<td>Right temporal</td>
</tr>
</tbody>
</table>

Table 13-1 Demographics of patient group undergoing frameless SEEG in this series
(NA not applicable)
13.3.2 Assessment of implantation accuracy

Figure 13-6 demonstrates the segmentation of electrodes for case 8, derived from post-operative CT, reconstructed on the 3D models and overlaid over the planned trajectories on the S7 Stealthstation. Overall qualitative and quantitative assessments are shown in Tables 13-2 and 13-3.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Number of Electrodes</th>
<th>Qualitative</th>
<th>Quantitative assessment (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Accurate targeting</td>
<td>TA</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>3</td>
<td>6.6 (7.3) 0 (0) 6.6 (7.3)</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>9</td>
<td>4.5 (7.5) 3.4 (9.2) 4.8 (8.8)</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>5</td>
<td>2.7 (5.2) 2.7 (6.9) 3.1 (5.6)</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>9</td>
<td>4.0 (8.5) 2.8 (5.3) 3.6 (5.9)</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>6</td>
<td>4.9 (9.9) 1.5 (2.9) 5.1 (8.9)</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>5</td>
<td>7.0 (10.5) 1.8 (3.1) 6.2 (8.7)</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>7</td>
<td>6.7 (10.4) 3.2 (6.2) 5.3 (8.7)</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>8</td>
<td>3.1 (5.4) 0.7 (1.4) 3.1 (6.3)</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>10</td>
<td>4.2 (8.7) 1.6 (4.2) 3.9 (7.2)</td>
</tr>
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<td>9</td>
<td>9</td>
<td>5.1 (6.3) 2.0 (6.4) 4.9 (7.2)</td>
</tr>
<tr>
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<td>10</td>
<td>10</td>
<td>4.6 (6.3) 1.5 (6.4) 4.3 (7.2)</td>
</tr>
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</tr>
<tr>
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<td>10</td>
<td>9</td>
<td>6.1 (8.2) 2.3 (5.2) 5.3 (6.4)</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>7</td>
<td>3.6 (8.6) 1.7 (4.1) 2.9 (6.3)</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>7</td>
<td>3.1 (5.9) 1.4 (3.2) 2.6 (5.5)</td>
</tr>
<tr>
<td>16</td>
<td>7</td>
<td>7</td>
<td>3.9 (7.4) 1.3 (2.4) 3.6 (5.3)</td>
</tr>
<tr>
<td>17</td>
<td>7</td>
<td>7</td>
<td>2.3 (4.8) 0.8 (1.4) 2.5 (5.7)</td>
</tr>
<tr>
<td>18</td>
<td>11</td>
<td>10</td>
<td>1.9 (5.4) 1.2 (5.8) 2.1 (3.7)</td>
</tr>
<tr>
<td>19</td>
<td>7</td>
<td>7</td>
<td>2.3 (5.2) 1.1 (1.3) 3.2 (4.7)</td>
</tr>
<tr>
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<td>10</td>
<td>10</td>
<td>1.3 (3.8) 1.2 (2.4) 1.6 (2.5)</td>
</tr>
<tr>
<td>21</td>
<td>8</td>
<td>8</td>
<td>1.0 (2.4) 1.0 (1.4) 1.3 (1.6)</td>
</tr>
<tr>
<td>22</td>
<td>13</td>
<td>13</td>
<td>2.7 (5.5) 1.7 (4.4) 3.3 (6.5)</td>
</tr>
</tbody>
</table>

Table 13-2 Outcomes of the quantitative and qualitative assessments of implantation
(TA trajectory accuracy, ED electrode deviation, EA electrode accuracy, L deviation of electrode length, Quantitative assessment expressed as mean and worst recorded figure for that patient in brackets).
Table 13-3 Mean electrode accuracy by electrode target

<table>
<thead>
<tr>
<th>Electrode Target</th>
<th>Number</th>
<th>Mean electrode accuracy (mm)</th>
<th>Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>16</td>
<td>2.76</td>
<td>3</td>
</tr>
<tr>
<td>Anterior Hippocampus</td>
<td>19</td>
<td>3.62</td>
<td>1</td>
</tr>
<tr>
<td>Posterior Hippocampus</td>
<td>19</td>
<td>3.31</td>
<td>1</td>
</tr>
<tr>
<td>Cingulate Gyrus</td>
<td>13</td>
<td>4.28</td>
<td>0</td>
</tr>
<tr>
<td>Orbitofrontal</td>
<td>16</td>
<td>4.47</td>
<td>0</td>
</tr>
<tr>
<td>Insula</td>
<td>15</td>
<td>2.83</td>
<td>4</td>
</tr>
<tr>
<td>Lateral Temporal</td>
<td>12</td>
<td>4.30</td>
<td>0</td>
</tr>
<tr>
<td>Frontal</td>
<td>22</td>
<td>3.38</td>
<td>2</td>
</tr>
<tr>
<td>Peri-rolandic</td>
<td>14</td>
<td>3.99</td>
<td>0</td>
</tr>
<tr>
<td>Parietal</td>
<td>27</td>
<td>3.85</td>
<td>1</td>
</tr>
<tr>
<td>Occipital</td>
<td>14</td>
<td>3.89</td>
<td>0</td>
</tr>
</tbody>
</table>

There were 187 electrodes inserted in total with 175 electrodes deemed to have reached their planned neurophysiological target. The mean electrode accuracy was 3.66 mm with a standard deviation of 2.21 mm, median 3.45 mm, IQR of 3.6 mm.

There was no significant difference between the accuracy of implantation of mesial temporal versus extratemporal electrodes. A quantitative comparison of EA values showed a tendency to improved EA values for mesial temporal electrodes, although this was not statistically significant (P=0.057, 2 tailed paired T test type 2). A qualitative comparison of target hitting showed no difference between mesial temporal and extra-temporal electrodes (P=0.33, Fisher exact test).

12 electrodes were deemed to have missed their neurophysiological targets, in cases 1, 3, 5, 6, 8, 12, 13 and 18. 4 of these electrodes were subject to significant extradural deflection and 3 of these were satisfactorily resited at a later date with accurate targeting. The extradural deflection occurred early on in our experience, prior to the use of a rigid stylette to
ensure dural breach and to create an intraparenchymal track. Table 13-4 summarises the details of all the missed electrodes. Figures 13-6 and 13-7 show examples of post-operative electrode reconstructions.

<table>
<thead>
<tr>
<th>Case</th>
<th>Electrode</th>
<th>Target</th>
<th>Electrode accuracy (mm)</th>
<th>Electrode depth (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amygdala</td>
<td>Inferiorly placed in entorhinal cortex</td>
<td>5.4</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>R parietal periventricular tuber</td>
<td>Anteriorly placed</td>
<td>7.3</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Amygdala</td>
<td>Inferiorly placed in entorhinal cortex</td>
<td>0.9</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>Anterior Hippocampus</td>
<td>Inferiorly placed</td>
<td>2.0</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>SFG to Anterior Insula</td>
<td>Extradural deflection: satisfactorily resited</td>
<td>1.8</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>Posterior Insula</td>
<td>Extradural deflection: unsatisfactorily resited</td>
<td>4.3</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>MFG to Superior lesion</td>
<td>Extradural deflection: satisfactorily resited</td>
<td>2.5</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>SFG to Lateral lesion</td>
<td>Extradural deflection: satisfactorily resited</td>
<td>3.6</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>Amygdala</td>
<td>Inferiorly placed in entorhinal cortex</td>
<td>6.8</td>
<td>36</td>
</tr>
<tr>
<td>12</td>
<td>Posterior Insula</td>
<td>Short and mesial placed in internal capsule</td>
<td>2.4</td>
<td>35</td>
</tr>
<tr>
<td>13</td>
<td>Posterior Hippocampus</td>
<td>Inferiorly placed</td>
<td>4.1</td>
<td>48</td>
</tr>
<tr>
<td>18</td>
<td>Posterior Insula</td>
<td>Mesially placed in striatum</td>
<td>2.6</td>
<td>55</td>
</tr>
</tbody>
</table>

*Table 13-4 The details of the electrodes deemed to have missed their neurophysiological targets*
Figure 13-6 Post-operative reconstruction of electrode implantation coregistered to the preoperative 3D multimodal models and displayed on StealthStation for patient 8

Figure 13-7 Post-operative reconstruction of electrode implantation on AMIRA software for patient 6, showing extradural deflection of electrode
13.3.3 Outcomes

16 patients have been offered cortical resections on the basis of recordings from the SEEG implantation. 6 patients have been excluded from definitive resective surgery based on the SEEG recordings. There was one haemorrhagic complication in case 18, evident on post-operative CT. The blood was in the sylvian cistern on the side of the implantation, with no obvious cause of bleeding. The patient was asymptomatic with no neurological deficits, and no further treatment was required. There were no cases of infection. All electrodes were removed following recording with no complications. One patient complained of chest pain following explantation, requiring inpatient assessment to exclude a pulmonary embolus and cardiac event. No underlying cause was found for the chest pain, and the patient made a full recovery.

13.4 Discussion

13.4.1 Summary

Burr hole biopsy of intracerebral tumours is routinely done using frameless stereotaxy in preference to frame-based methods, although it is generally accepted that frameless techniques confer lower degrees of accuracy of registration (Price, 2003). This technique confers a level of precision that is considered acceptable for the majority of cases. Of course there remain indications for frame-based biopsy, such as deep seated small tumours, when the added precision is necessary.

This situation is analogous to SEEG, where multiple electrodes are placed into relatively broad targets. The twin concerns with SEEG are accurate targeting and avoidance of cortical blood vessels. We believe that in selected cases, electrode arrangements can be designed with the necessary safety profile for implementation with a frameless technique. The main benefit this confers is a seamless integration into the surgical workflow, without the need for additional equipment, support and expertise.
Mehta describes the frameless delivery of depth electrodes through burr holes and craniotomy sites, using a slotted, custom-designed adaptor built to interface with a commercially available neuronavigation system (StealthStation Guide Frame-DT and 960-525 StealthFighter) (Mehta et al., 2005). The need for burr holes has several disadvantages, limiting the number of electrodes that can be placed at any one time and limiting the subsequent design of any bone flap in the future. Also larger openings generally predispose to increased risks of post-operative infection.

Shamir assessed the accuracy of delivery of the Ommaya ventricular catheter using the Medtronic neuronavigation system in 15 consecutive cases, comparing the implemented plan to the planned trajectory (Shamir et al., 2011). They found a mean target point localisation error of 5.9+4.3 mm, and a mean shift of 3.9+4.7 mm.

The technique in our case series relies on custom-designed reducing tubes and a hammered divot in the cranial outer table to stabilise the drilled trajectory. With this technique, frameless SEEG delivered 175/187 electrodes to their expected target, with a mean electrode accuracy of 3.66 mm. There was improvement in implementation with experience; in the first half of the series (11 patients) 9 electrodes missed their neurophysiological target, whilst in the second half of the series only 3 electrodes missed their target. Most importantly there were no serious haemorrhagic complications, although we deliberately avoided trajectories that require finer accuracy, such as the trans-sylvian route to the insula. Finally, this technique confers a level of flexibility, where it is straightforward to augment an implantation with additional electrodes if further contacts are required. This was performed in patient 14 with no complications, when the initial implantation failed to yield enough information to guide treatment, and the additional information proved valuable to the case.

An important note of caution should be made that for each patient the worst recorded electrode accuracy is a further guide to accuracy. Using these figures it is clear that wide
safety margins (1cm) need to be incorporated to provide a level of safety required in clinical practice.

There was no significant difference between the accuracy of electrode insertion between mesial temporal and non-mesial temporal electrodes. There was however a tendency towards more accurate quantitative implantations in the amygdala and hippocampus. This may be due to these electrodes being very commonly placed, and being placed perpendicular to the skull. Qualitatively, however, 5 of the 12 missed targets were in the mesial temporal structures. This is most likely due to the fact that these targeted structures are well-defined and smaller than other, more extensive extratemporal targets.

13.4.2 Limitations
The greatest source of inaccuracy is the registration in frameless stereotaxy. The registration error associated with frameless stereotaxy is well documented, and does not necessarily correlate with the registration error generated by the system (Wang and Song, 2011). In our series we used scalp fiducial marker registration, and made great effort to achieve the best registration possible. We anticipate that the use of bone fiducials should further increase the accuracy of the registration and the procedure in total, although this would also increase the presurgical invasiveness of the procedure.

Further deterioration in electrode accuracy occurs with the drilling of the trajectory and intracranial electrode deviation. Drill trajectory was stabilised by a hammered divot in the outer table and a system of reducing tubes to deliver the drill and the bolt in a stereotactic manner. It is postulated that this could be further improved using robotic assistance. With regard to electrode deviation, changes were made to the technique during the series as experience was acquired. Of the 12/187 electrodes that missed their target, 4 electrodes deviated significantly during their intracranial course. This deviation was mainly caused by extradural deflection, and 3 electrodes were satisfactorily resited through the same bolt at a later date. In addition, some electrode deviation was observed intraparenchymally following
large white matter tracts, due to the non-rigid nature of the electrodes. From the seventh case onwards, a rigid stylette was passed through the bolts prior to each electrode. This prevented any further extradural deflections and reduced clinically relevant electrode deviations.

Our case series is further limited by inaccuracies in the assessment of electrode placement.

The qualitative assessment relies on the registration of a post-operative CT scan with a pre-operative MRI scan, and rendering of the electrodes in the context of the cortical segmentation. This registration is limited by the issue of brain shift, with escape of CSF during electrode implantation. This could be addressed in the future by the acquisition of post-operative MRI scans, although we would not anticipate significant shift with this procedure. The necessary safety testing for the acquisition of post-operative MRI in this patient group is now complete in our centre.

The quantitative assessment used a technique first described by Shamir et al in the placement of ventricular access devices (Shamir et al., 2011). The electrode accuracy is a measure of lateral shift perpendicular to and at the point of the planned trajectory target. This is not the same as the target point localisation error referred to elsewhere, that is the Euclidean distance between the planned trajectory target and the implemented electrode tip (Cardinale et al., 2013). The tip of the electrode is not the only point of interest in the implantation, as recordings are made from all contacts along the length of the electrodes, and our measure of electrode accuracy is sufficient to gauge electrode delivery. Unfortunately using the AMIRA software it was not possible to extract the Euclidean distance from the electrode and planned target points, although this functionality is now available using the EpiNav™ software.
13.4.3 Further work

The implementation of frameless SEEG can be further improved in a number of ways. The use of bone fiducials should reduce the registration errors (Holloway et al., 2005). The incorporation of a robotic platform to deliver trajectories should improve the delivery of the trajectory by more accurate targeting and drilling. Using EpiNav™, it will then be possible to calculate the euclidean distance between planned and implemented trajectories at both the target point and entry point on the cortical surface of the brain. The overall aim should be to achieve a level of accuracy equivalent with frame-based techniques.

13.5 Conclusion

In summary, our technique of frameless SEEG is a feasible approach in selected cases when a safety margin can be incorporated. The ease of implementation makes this approach particularly attractive for centres moving towards adoption of SEEG in the presurgical evaluation for epilepsy. However, the inferior accuracy of this method makes it less suitable for implantations of ‘high-risk’ trajectories, which are best achieved with a conventional, frame-based technique.

A general comparison of frame-based versus frameless stereoEEG is shown in table 13-5.
<table>
<thead>
<tr>
<th></th>
<th>Framed-based SEEG</th>
<th>Frameless SEEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for frame</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Need for intra-operative imaging</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Accuracy to target</td>
<td>&lt;2mm</td>
<td>&gt;2mm</td>
</tr>
<tr>
<td>Stability of tool delivery</td>
<td>Excellent</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Suitability for high risk trajectories</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Uniformity of method</td>
<td>Varies between centres</td>
<td>Not previously described</td>
</tr>
<tr>
<td>Software</td>
<td>Varies between centres</td>
<td>Medtronic StealthStation</td>
</tr>
<tr>
<td>Restrictions to surgical field</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Flexibility to change plans intra-operatively</td>
<td>Limited</td>
<td>Good</td>
</tr>
<tr>
<td>Ease of implementation</td>
<td>Limited</td>
<td>Good</td>
</tr>
</tbody>
</table>

*Table 13-5 Comparison of frame-based versus frameless SEEG*
14 Meyer’s loop asymmetry and language lateralisation in epilepsy

14.1 Introduction

White matter connections can be delineated and quantified in vivo using diffusion MRI and tractography (Yamada et al., 2009, Keller et al., 2014). Asymmetry of white matter tracks is well-described, with larger left than right corticospinal tracts in group analyses (Thiebaut de Schotten et al., 2011).

The literature on arcuate fasciculus asymmetry is mixed. In individual subjects, some studies have shown a correlation between the volume of the arcuate fasciculus tract and language lateralisation, determined by the Wada test (Matsumoto et al., 2008) and by functional MRI (fMRI) (Sreedharan et al., 2015), whilst others have not found a consistent association (Propper et al., 2010). Recent work suggests the fasciculus may in fact be composed of two parallel tracts, with independent associations to language dominance (Catani et al., 2005, Thiebaut de Schotten et al., 2011).

Meyer’s loop is the anterior bundle of the optic radiation, a white matter tract that makes up part of the visual pathway. Meyer’s loop runs from the lateral geniculate nucleus (LGN) of the thalamus, passes anteroinferiorly over the temporal horn of the lateral ventricle, and then sharply turns posteriorly to join the central and posterior bundles of the optic radiation heading towards the occipital cortex. There is considerable interindividual variability in the anterior extent of Meyer’s loop (Mandelstam, 2012), as shown in both anatomical studies (22 to 37mm from the temporal pole (Ebeling and Reulen, 1988)) and probabilistic tractography (24-47mm from the temporal pole (Yogarajah et al., 2009)). Meyer’s loop is at risk with anterior temporal lobe resections, and is therefore of great interest in epilepsy surgery.

In a recent study deterministic tractography was applied to 20 healthy right-handed volunteers, to look for asymmetry in the anterior extent of Meyer’s loop in individual subjects...
(Dreessen de Gervai et al., 2014). A significant asymmetry was found, with mean Meyer’s loop-temporal pole distances measured as 39.7mm on the left and 45.5mm on the right. This asymmetry is supported by probabilistic tractography studies, which have similarly reported a trend towards more anteriorly placed Meyer’s loops in the left temporal lobe (Yogarajah et al., 2009). This concurs with the finding that visual field defects are 3.5 times more likely with left-sided than right-sided anterior temporal lobe resections (Jeelani et al., 2010), despite the fact that left sided resections are normally more conservative to preserve neurocognitive function. (Penfield and Baldwin, 1952).

In this study we test the hypotheses that: 1. Asymmetries in the anterior extent of Meyer’s loop are associated with language lateralisation, as the structural correlates associated with language development may result in displacement of Meyer’s loop to a more anterior location. 2. Arcuate fasciculus volume is correlated with language lateralisation in individuals with focal epilepsy.

14.2 Method

14.2.1 Subjects and recruitment

This project was approved by the Joint Research Ethics Committee of the National Hospital for Neurology and Neurosurgery (NHNN), and University College London (UCL) Institute of Neurology (ION). All participants were provided with patient information sheets and gave written, informed consent.

All subjects had medically refractory focal epilepsy, and were undergoing presurgical evaluation at the National Hospital for Neurology and Neurosurgery. Subjects were selected based on the acquisition of language fMRI studies and diffusion MRI acquisition at the National Epilepsy Society (ES) between August 2010 and August 2013. The group was selected to give an enriched, roughly even distribution of left and non-left language dominance. This enables a testing of the hypothesis, but is not reflective of the normal
population, in whom language is predominantly on the left side. All analyses were carried out in a blinded fashion.

61 patients were identified with language fMRI and diffusion MRI acquisition. 4 patients were excluded from further analysis as they had large mass lesions that distorted the location of Meyer’s loop. The demographics of the remaining 57 patients are shown in the table below. 54 patients had a diagnosis of temporal lobe epilepsy, and three patients had extratemporal epilepsy. The majority of subjects did have radiological lesions shown on imaging, but none had structural pathology that affected the location of Meyer’s loop. For the purposes of this study, left language dominance is defined by fMRI as a lateralisation index of 0.4 or above using the verbal fluency paradigm and non-left language dominance is defined as a lateralisation index of below 0.4 (Briellmann et al., 2003, Williams et al., 2012).
<table>
<thead>
<tr>
<th>Language</th>
<th>Number</th>
<th>Median age (range)</th>
<th>Sex (M/F)</th>
<th>Median duration (range) in years</th>
<th>Side of epilepsy (R/L)</th>
<th>Lesional</th>
<th>Handed (R/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-left</td>
<td>21</td>
<td>38 (20-56)</td>
<td>10/11</td>
<td>16 (1-33)</td>
<td>11/10</td>
<td>TOTAL- 18 (86%)</td>
<td>11/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNET- 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HS- 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FCD- 2</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>36</td>
<td>38 (19-58)</td>
<td>14/22</td>
<td>17 (1-44)</td>
<td>14/22</td>
<td>TOTAL -30 (83%)</td>
<td>31/5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DNET- 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HS- 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FCD- 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dual path – 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cavernoma- 1</td>
<td></td>
</tr>
</tbody>
</table>

Table 14-1 Demographics of the study population (M-male, F-female, R-right, L-left, DNET- dysembryoplastic neuroepithelial tumour, HS- hippocampal sclerosis, FCD- focal cortical dysplasia, Dual path- dual pathology)

14.2.2 MRI acquisition

Functional MRI and diffusion MRI scans were performed on a 3T GE Excite II scanner (General Electric, Waukesha, Milwaukee, WI).

For functional MRI, gradient echo echoplanar images provided blood oxygen level-dependent contrast, and each volume comprised 36 contiguous oblique axial slices of 2.4mm thickness. The field of view of 24×24 cm was acquired with a 64×64 matrix that was zero-filled to 64×64 for a voxel size of 3.75×3.75×2.5 mm. Sequence timings were TE/TR = 22./2500 ms, with parallel imaging factor 2.
For diffusion MRI, data were acquired using a cardiac-triggered single-shot spin-echo echo planar imaging sequence with echo time (TE) of 74.7 ms, with parallel imaging factor 2. 60 contiguous axial slices of 2.4mm thickness were obtained covering the whole brain, and diffusion-weighting gradients were applied in 52 non-collinear directions (Cook et al., 2007) with a b-value of 1200 s/mm², along with six non-diffusion weighted scans. The field of view of 24×24 cm was acquired with a 96×96 matrix that was zero-filled to 128×128 for a voxel size of 1.875×1.875×2.4 mm.

In addition, a 3D T1-weighted Fast Spoiled Gradient-Recalled (FSPGR) image was acquired with a field of view of 187×240×240 mm (AP×LR×IS) and a 170×256×256 acquisition matrix for a 1.1×0.94×0.94 mm voxel size. Sequence details include: TE/TR/TI = 3.06/8.14/450 ms, flip angle 20°, parallel imaging acceleration factor 2.

14.2.3 Functional MRI language paradigm

Each subject performed a verbal fluency language task. This consists of a blocked experimental design with 30 seconds activation blocks alternating with 30 seconds of cross-hair fixation during the baseline condition over 5.5 minutes. This paradigm is known to reliably lateralise expressive language (Powell et al., 2006). For this paradigm subjects were asked during the activation phase to covertly generate different words beginning with a visually presented letter (A, S, W, D and E) contrasted by crosshair fixation as rest condition. This paradigm was used to identify language regions in the inferior and middle frontal gyri (Woermann et al., 2003, Liegeois et al., 2004).

14.2.4 Functional MRI preprocessing and LI calculation

The verbal fluency paradigm, used in clinical practice (Gaillard et al., 2004), was analysed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Imaging time series were realigned, normalised into standard anatomical space and smoothed. An anatomical mask
incorporating the inferior frontal and middle frontal gyri was used. A bootstrap method was employed to calculate lateralisation indices (LI) within the mask in all patients using the SPM8 LI toolbox.

14.2.5 Diffusion Preprocessing

The diffusion MRI scans were transferred to a Linux workstation, and corrected for eddy current correction distortion using the eddy_correct tool in FSL (Smith et al., 2004). Data was processed using the MRtrix software package 0.2.12 (http://www.brain.org.au/software/) to produce a fractional anisotropy (FA) map, directionally-encoded colour map and constrained spherical deconvolution (CSD) fibre orientation distributions (Farquharson et al., 2013, Jeurissen et al., 2010, Tournier et al., 2012a, Jeurissen et al., 2013). CSD is a higher order model for estimating fibre orientations, which uses high angular resolution diffusion-weighted imaging data and can resolve multiple fibre populations within each imaging voxel. We used a maximum harmonic order (Lmax) of 8, and obtained single fibre response functions from all voxels in the brain with FA values of 0.7 or higher.

14.2.6 Tractography

Tractography was carried out using probabilistic tractography in MRtrix (using the SD_PROB command), using a minimum curvature radius of 1 mm, a step size of 0.2 mm, and a minimum FOD amplitude of 0.1, to generate 1000 tracts from the seed region that met all inclusion and exclusion criteria. Regions of interest used to carry out tractography of optic radiation and arcuate fasciculus are described in figures 14.1 and 14.2.
Regions of interest indicated in yellow for optic radiation tractography

A- The seed region was the lateral geniculate nucleus, identified on axial slices of the FA map by locating the optic chiasm and following the post-chiasmal optic tracts posteriorly as they enter the thalamus. This was corroborated by identifying the transition of the posterior limb of the internal capsule to the cerebral peduncle. A generous seeding was undertaken, incorporating 4x4 voxels over 2 consecutive axial slices.

B- The waypoint was the stratum sagittale, identified posterior to the splenium of the corpus callosum at the level of the occipital horns of the lateral ventricle on the sagittal plane. Generous seeding was undertaken in a single coronal plane, with particular attention to include the inferior bundles that derive from the anterior Meyer’s loop.

C- A midline exclusion mask in the sagittal plane was added to exclude apparent tracts that cross the midline.

D- Tractography was run with these regions of interest to determine the anterior extent of the Meyer’s loop. A frontal exclusion mask in the coronal plane was then added to remove artefactual connections to adjacent white matter tracts such as the inferior longitudinal fasciculus and the uncinate fasciculus

E- Resulting tractography after addition of frontal exclusion mask.
Figure 14-2 Regions of interest indicated in yellow for arcuate fasciculus tractography
Regions of interest were generated in native space on directionally-encoded colour map in MRtrix. L-left
A,B-The seed region was the vertical limb of the fasciculus, identified as blue voxels, indicating vertical diffusion vectors, in the middle of the C-shaped tract on the sagittal planes of the coloured FA map (A). The seed is generated in the axial plane (B).
C,D-The waypoint was the inferior frontal gyrus, identified as red (left-right diffusion vectors) voxels in the sagittal plane of the coloured FA map (C). The seed is generated in the coronal plane (D).
A midline exclusion mask was added to exclude connectivity that crossed the midline.
E,F-Resulting tractography of arcuate fasciculus in the sagittal and coronal plane (yellow).

The resulting tract files were converted into a map of the fraction of tracts to intersect each voxel. The tract maps of arcuate fasciculi were thresholded at 5%, representing a compromise between retaining anatomically valid tracts and removing artefactual connections. The optic radiations were exported in nifti format to EpiNav™.(Centre for Medical Imaging and Computing, UCL, London). For display purposes, the optic radiations were thresholded individually, steadily increasing the threshold in an iterative process from 1% until the most anterior extent of the Meyer’s loops begins to recede.
14.2.7 Volumetric analyses

The volume of the arcuate fasciculus and optic radiation tracts were assessed in FSL using the thresholded tract maps. A measure of volumetric asymmetry of the arcuate fasciculus tracts was calculated using the formula:

\[
\text{Volume asymmetry} = \frac{V^L - V^R}{V^L + V^R}
\]

\(V^L\)-Volume of LEFT tract

\(V^R\)-Volume of RIGHT tract

This data was not corrected.

14.2.8 Meyer’s loop asymmetry

The distance from the anterior border of Meyer’s loop to the temporal pole was measured in EpiNav™. The FA map was rigidly coregistered to the 3D T1-weighted image, and used to warp the optic radiation tracts to the T1. The axial plane was tilted to run along the longitudinal axis of the hippocampi, and the distance from Meyer’s loop to the temporal pole and from temporal horn to temporal pole was measured along this plane (Yogarajah et al., 2009) (figure 14.3).

Uncorrected Meyer’s loop asymmetry was calculated using the formula:

\[\text{MLA} = M^L - M^R\]

\(M^L\)-Distance of LEFT Meyer’s loop to temporal pole

\(M^R\)-Distance of RIGHT Meyer’s loop to temporal pole

This value was corrected to account for interindividual variations in head size, using the formula:

\[\text{Corrected MLA} = \frac{(M^L - M^R)}{L}\]
L- Distance of temporal pole to occipital pole

Figure 14-3 Measurement of optic radiation tractography asymmetry
A- Oblique axial view of 3D T1-weighted MRI with optic radiation tractography surface models (yellow-right, pink-left) overlaid
B- Sagittal view of right optic radiation surface model (pink) with axial plane tilted to longitudinal axis of hippocampus, and Meyer's loop-temporal pole distance shown (dotted blue line).
C- 3D surface models of left and right optic radiations

14.2.9 Statistics

Patients were removed from analysis if there was a demonstrable failure of tractography to identify Meyer's loop due to the presence of large mass lesions. Remaining patients were grouped as left language dominant if LI was greater than 0.4 (left dominant), and non-left language dominant if LI was less than 0.4 (non-left dominant) (Briellmann et al., 2003).

Statistical analysis was performed with IBM SPSS software (Version 22). Independent sample T-tests were employed to look for significant differences between the groups with a Bonferroni correction for the two prime hypotheses, and a Pearson correlation coefficient was calculated to assess for any linear correlations.
14.3 Results

Intra-rater and inter-rater variability for tractography was assessed using mean Dice similarity overlap of thresholded tracts from 5 subjects, where 1 represents complete overlap and 0 represents no overlap (Crum et al., 2006). The mean intra-rater DICE overlap was 0.76 for the arcuate fasciculus and 0.69 for the optic radiation. The mean inter-rater DICE overlap was 0.72 for the arcuate fasciculus and 0.74 for the optic radiation. These values are in the same range of, or higher than, scan-rescan reproducibility tests on CSD-based tractography (Kristo et al., 2013). The intra-rater and inter-rater variability in the metrics derived from optic radiation tractography were assessed using intraclass correlation coefficients (ICC) between 5 subjects. The ICC for Meyer loop asymmetry and temporal horn asymmetry for the same user was 0.99 and 0.99 respectively, and between different users was 0.94 and 0.99.

Figure 14.4 shows the Pearson correlation for corrected MLA against language lateralisation in the whole group. There was a negative linear correlation, with greater left lateraliised language associated with more anteriorly placed left Meyer’s loops (R value -0.34, p=0.01). There was no linear correlation between language lateralisation and arcuate fasciculus asymmetry (Figure 14.5) or temporal horn asymmetry.
Figure 14-4 Scatterplot of corrected Meyer’s loop asymmetry (MLA) against language lateralisation

Figure 14-5 Scatterplot of arcuate fasciculus asymmetry (AFA) against language lateralisation
Verbal fluency LI +1 = entirely left activation. -1 = entirely right activation
In the total group, the mean distance from the anterior border of Meyer’s loop to the temporal pole was 31.19mm (standard deviation 6.35mm, range 19.5-48.8mm) on the left, and 32.10mm (standard deviation 6.34mm, range 17.40-46.50mm) on the right.

The mean distance of Meyer’s loop behind the temporal horn was 3.28mm (standard deviation 7.18, range 20.10mm behind to 28.80mm in front) on the left, and 5.27mm (standard deviation 6.32, range 30.2mm behind to 3.1mm in front) on the right.

The mean asymmetries in Meyer’s loop, temporal horn and arcuate fasciculi volumes for the left and non-left language dominant groups are shown in Table 14.2. There was a significant difference in corrected Meyer’s loop asymmetry, with the left loop being anterior to the right loop in the LI>0.4 group, and posterior to the right loop in the LI<0.4 group (p=0.003) (Figure 14.6). There was no significant temporal horn asymmetry in either group. Arcuate fasciculus volumes were marginally greater on the left in both the LI>0.4 group (21600mm³ v 19900mm³) and the LI<0.4 group (19000mm³ v 17600mm³), with no significant difference between the LI>0.4 and LI<0.4 groups.

No significant differences were seen in MLA when considering the lateralization of the epilepsy (p=0.75), the presence of a lesion (p=0.71), or gender (0.93). An association between MLA and handedness is significant (p=0.024), reflecting the well-established relationship between handedness and language lateralisation (Pujol et al., 1999). No correlation was seen with age (R 0.59, P=0.66) or duration of epilepsy (R -0.05, P=0.97).
<table>
<thead>
<tr>
<th>Variable</th>
<th>LI&gt;0.4</th>
<th></th>
<th>LI&lt;0.4</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>MLA (mm)</td>
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<td>7.47</td>
<td>2.64</td>
<td>8.92</td>
<td>0.02*</td>
</tr>
<tr>
<td>Corrected MLA</td>
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<td>0.083</td>
<td>0.40</td>
<td>0.12</td>
<td>0.003*</td>
</tr>
<tr>
<td>THA (mm)</td>
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<td>11.54</td>
<td>1.89</td>
<td>8.75</td>
<td>0.69</td>
</tr>
<tr>
<td>AFA</td>
<td>0.04</td>
<td>0.14</td>
<td>0.01</td>
<td>0.16</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Table 14-2 Mean asymmetries in the left and non-left language groups (MLA-Meyer’s loop asymmetry Corrected MLA- corrected Meyer’s loop asymmetry, THA- temporal horn asymmetry, AFA- arcuate fasciculus asymmetry, LI- language lateralisation index, SD- standard deviation, * statistical significance at p<0.025 with Bonferroni correction)

Figure 14-6 Axial view of fMRI statistical maps with optic radiation tractography and verbal fluency BOLD activation
Optic radiation tractography (yellow- right, pink- left) and verbal fluency BOLD activation thresholded (orange) (L-left)
A- patient with left-dominant language (LI 0.83), and anteriorly placed left Meyer’s loop (MLA -14.9mm)
B- patient with non-left dominant language (LI 0.37), and posteriorly placed left Meyer’s loop (MLA 0.7mm)
14.4 Discussion

14.4.1 Summary of main findings

We performed optic radiation tractography in 57 subjects with TLE, using a probabilistic multi-fibre tractography method (constrained spherical deconvolution).

The mean distance of Meyer’s loop to the temporal pole was 31mm, although there was great variability between subjects, and also from one side to another.

In this study we examined the issue of MLA in a population with epilepsy and a reasonable distribution of language lateralisation determined by fMRI. We found a correlation between language lateralisation and MLA, with the left language dominant group having anteriorly placed Meyer’s loops on the left side and the non-left language dominant group having anteriorly placed Meyer’s loop on the right side. We found no correlation between arcuate fasciculus volume and language lateralisation.

14.4.2 Comparison with previous data

There are a large number of previous optic radiation tractography studies, but these are limited by either low subject numbers or the use of deterministic tractography methods, which are recognized to underestimate the anterior extent of Meyer’s loop (Farquharson et al., 2013, Lilja et al., 2015, Lilja et al., 2014). The group results in this study support the findings of dissection studies and other probabilistic tractography studies in terms of the anterior extent and variability of Meyer’s loop in all subjects (Lilja et al., 2014, Winston et al., 2014).

In the left language dominant group we found anteriorly placed Meyer’s loops on the left side, with a mean distance of 30.3mm from the temporal pole on the left and 33.1mm on the right, giving an asymmetry of -2.8mm. This is broadly consistent with the findings of a previous deterministic study, which showed a mean of 39.7mm on the left and 45.5mm on
the right, and an asymmetry of -5.8mm (Dreessen de Gervai et al., 2014). However, the use of deterministic tractography in their study is likely to have resulted in an underestimation of the anterior extent of Meyer's loop. This is also consistent with the finding that visual field defects are more commonly seen with left-sided anterior temporal lobe resections, as the majority of patients are left language dominant (Jeelani et al., 2010).

In the non-left language dominant group, we found that Meyer’s loop is posteriorly placed on the left side in the non-left language group, with a mean distance of 32.8mm on the left and 30.3mm on the right, giving an asymmetry of 2.6mm. We are not aware of previous reports of MLA in a non-left language dominant group.

In this study we did not find a linear relationship between the arcuate fasciculus tractography volumes and the language lateralisation indices. This is in agreement with previous earlier work (Catani et al., 2005), which suggests that functional lateralisation correlates better with the number of streamlines in the arcuate fasciculus and the fractional anisotropy. However more recent studies have demonstrated a correlation between arcuate fasciculus volumes and language lateralisation in both healthy subjects (James et al., 2015, Sreedharan et al., 2015) and patients (Matsumoto et al., 2008). Interpretation of these studies is limited by the low number of subjects with atypical language lateralisation, which makes up a large proportion of our own series.

14.4.3 Limitations

In this study we used verbal fluency fMRI to determine measures of language lateralisation. This is a well-established paradigm that gives reasonable correlation with the Wada test in patients with epilepsy (Arora et al., 2009, Benke et al., 2006, Dym et al., 2011). However, it is limited in that it represents frontal hemispheric specialisation with no reliable temporal activation. Recognizing this we are developing auditory and visual naming paradigms that primarily activate temporal neocortex and this will lead to a future comparative study with the
anatomy of temporal lobe structures. We anticipate finding a stronger association between temporal activation and MLA.

A further limitation to this study is that the subjects all had focal epilepsy, and do not represent the healthy population. It is established that epilepsy causes white matter changes, associated with the development of epileptogenic networks (Luat and Chugani, 2008). For example, patients with temporal lobe epilepsy exhibit a global reduction in the volume of white matter tissue across frontal, temporal and parietal but not occipital lobe regions (Hermann et al., 2003). It is possible that localised microstructural anatomic-functional disturbances present in epilepsy may affect both language lateralisation and MLA and may not be seen in the normal population. It is therefore necessary to evaluate this association in healthy subjects. The reason for conducting this study in patients with epilepsy first is because the data was freely available, with a reasonable distribution of LI values to investigate the hypothesis.

A possible confounding factor in our series is that our tractography of the arcuate fasciculus may have failed to differentiate between different components (Matsumoto et al., 2008). The well-established direct pathway typically shows strong leftward lateralisation in right handed subjects, whereas the indirect pathway, consisting of the anterior and posterior segments, show rightward and no lateralisation respectively (Thiebaut de Schotten et al., 2011). Although there is evidence that seizure networks affect arcuate fasciculi bilaterally (Kim et al., 2011) a more tailored approach to tractography may give a different correlation with language lateralisation in patients with epilepsy.

14.4.4 Neurobiological implications

The temporal horn is not a reliable marker for the anterior extent of Meyer’s loop. Meyer’s loop is commonly posterior to the temporal horn although there are subjects in whom it extends anterior to the temporal horn. Thus the surgeon has to take an individually tailored approach to anterior temporal lobe resections in order to avoid injury to the optic radiation,
and a consequent visual field defect, and this may be aided by the use of pre- or intra-operatively acquired tractography (Winston et al., 2014). In the future it is hoped that fMRI data for language and memory paradigms can be similarly incorporated into surgical planning, to allow for a tailored resection that preserves function. This would be far superior to the one size fits all approach, that is is currently employed to determine extent of ATLR according to hemisphere dominance.

The finding that MLA may be associated with language lateralisation, as determined by verbal fluency fMRI, supports the hypothesis that language lateralisation is related to the architecture of the anterior temporal lobe. This adds to the literature on brain asymmetry, and the relationship between functional and structural lateralisation. We cannot ascribe cause and effect, or conclude whether language dominance influences the anatomy of the optic radiation in the anterior temporal lobe or vice-versa. We also cannot ascribe handedness from MLA. However, there is growing evidence that lateralisation begins at the level of molecular genetic level (Karlebach and Francks, 2015, Francks, 2015), and continues through to asymmetries in microcircuitry (Galuske et al., 2000) and processing (Chance, 2014). The observations of functional and macrostructural lateralisation are likely to reflect the endpoints of these complex developmental processes.

14.5 Conclusion

In conclusion we present further evidence for intrasubject asymmetry in the anterior extent of Meyer’s loop, and demonstrate a linear relationship between the extent of this asymmetry and the lateralisation of language determined by verbal fluency fMRI in patients with epilepsy. Further work should aim to evaluate this association in a healthy control population and to employ other language paradigms that primarily activate the temporal lobe.
15 Overall conclusions

15.1 Main Findings and Contribution

The main findings and contributions from each study are given below:

Chapter 10 How widespread is the use of 3D Multimodality Integrated Models in Epilepsy Surgery practice?

- The national and international uptake of 3DMMI is poor, and does not form part of routine clinical practice in epilepsy surgery.
- In centres that do practice 3DMMI, there is no consensus on what software to use for image integration.
- There is demand for the increased use of 3DMMI in clinical practice.
- The main barriers to adoption of 3DMMI appear to financial cost and expertise needed for image integration.
- Availability of software, ease of use and cheap cost of implementation would increase the use of 3DMMI in clinical practice.

Chapter 11 Utility of 3D multimodality imaging in the implantation of intracranial electrodes in epilepsy

- It is possible to perform 3DMMI in all patients undergoing presurgical evaluation for ic-EEG, as part of a routine clinical pipeline, using AMIRA or EpiNav™ software.
- Disclosure of 3DMMI to neurologists leads to the fine-tuning of strategies to design intracranial electrode implantations.
- Disclosure of 3DMMI to surgeons leads to changes in precise surgical planning of SEEG implantations, with changes in entry and target points.
- In all cases disclosure of 3DMMI informs decision-making and is considered a valuable tool during presurgical evaluation and surgical management.
Chapter 12 Comparison of computer-assisted and manual planning in the implantation of intracranial depth electrodes in epilepsy

- The precise planning of intracranial depth electrode implantations is amenable to computer assistance.
- A computer-assisted multi-trajectory planner has been developed for use in EpiNav™ software.
- Use of the multi-trajectory planner leads to statistically significant improvements in safety and grey/white matter capture compared with conventional manual planning.
- Use of the multi-trajectory planner is associated with substantial savings in time within the framework of a 3D multimodality model, with the median duration of CAP taking 8 minutes.
- The majority of trajectories generated by the multi-trajectory planner are feasible for surgical implementation. However, all trajectories need to be checked by the surgeon.
- CAP is likely to be most useful as a starting point to the planning process, prior to manual checking and adjustment.

Chapter 13 A novel method for implementation of frameless stereoEEG in epilepsy surgery

- It is feasible to implement SEEG with frameless neuronavigation.
- Frameless SEEG delivers depth electrodes with mean target point accuracy of 3.66mm.
- This technique is not suitable for trajectories that are considered ‘high-risk’.
- Frameless SEEG does not require additional hardware, and is easy to implement in other centres.
- Further work is needed to deliver more accurate trajectories that are comparable with frame-based techniques.

Chapter 14 Meyer's loop asymmetry and language lateralisation
There is considerable intersubject variability in the anterior extension of Meyer’s loop in the temporal lobe.

There is a linear correlation between intrasubject MLA and language lateralisation determined by verbal fluency fMRI, with the dominant hemisphere related to more anteriorly located Meyer’s loop.

There is no evidence of significant temporal horn asymmetry within subjects.

EpiNav™ is a flexible software platform for image integration and advanced visualisation that permits research in neuroimaging.

Chapters 11-14 Use of EpiNav™

- Image integration and 3D visualisation can be performed in EpiNav™ in routine clinical practice.
- It is feasible to plan depth electrode implantations in the EpiNav™ trajectory planner, and to export these plans to the Medtronic S7 Stealthstation for clinical implementation.
- Implanted depth electrodes can be reconstructed within the 3D multimodality framework using EpiNav™.
- It is feasible to use advanced segmentation tools to plan resection volume in patients with extratemporal epilepsy.
- EpiNav™ provides the foundation for an integrated image-guided solution to the surgical management of epilepsy, and has been disseminated to 4 other centres for trial use.

15.2 Limitations

The broad aim of this thesis was to examine ways in which the presurgical evaluation and surgical planning for epilepsy can be optimised and simplified with novel imaging techniques and translational methods. This work has been performed at the Department of Clinical and Experimental Epilepsy (DCEE) and the Department of Neurosurgery, National Hospital for
Neurology and Neurosurgery, with software support provided by the Translational Imaging Group, CMIC. This represents a controlled environment, which has several advantages in implementing image-guided solutions in epilepsy surgery. These advantages are described in more detail below.

15.2.1 Engagement
This work took place within a well-defined organisational framework, which was particularly conducive to our research aims. There was full engagement with all member of the multi-disciplinary team, including neurophysiologists, neurologists, neurosurgeons, software developers and other research personnel. In addition, our work was supported with monthly meetings that provided an overview on the direction of the work. Clearly, epilepsy surgery is a complex pathway that requires excellent communication between clinicians over extended periods of time. For successful implementation of new imaging techniques and translational methods in this environment, widespread engagement amongst team members is critical.

15.2.2 Experience
We have an internationally respected epilepsy surgery programme. We established the integration of multimodal brain imaging data in 3-dimensions for planning surgery, and this has been part of the routine clinical pathway for patients undergoing ic-EEG for over 4 years. The advantages this confers includes the availability and use of different imaging modalities in presurgical evaluation and the knowledge of how to use this in clinical decision-making. Transferring these data into the operating theatre requires additional support, and MRI physicists are essential for this.

15.3 Dissemination
Optimisation and simplification of the epilepsy surgery pipeline are two stated aims of this project. We believe that using 3DMMI confers great benefits, but that these benefits are unlikely to be realised in clinical practice if they can only be achieved with complex, high cost
pipelines. There is a balance to be struck between optimising solutions and making them simple to use. A solution that is highly precise but unworkable in clinical practice is of little use. Similarly, a solution that is imprecise but easy to implement is also compromised.

Striking the right balance can be challenging to do for individual centres, especially if they do not share the same levels of engagement and experience. Implementing 3DMMI in this environment therefore presents a different set of challenges.

15.3.1 Challenges

15.3.1.1 Interpretation of 3DMMI
The benefits of displaying data in integrated 3D models are described in chapter 11. One of the key findings is that this ‘democratises’ knowledge, generating brain models with regions of interest that are easy to understand. This is particularly clear when one shows the results of 3DMMI to patients to communicate risk.

However, the risks with this technique are that the end-user may fail to appreciate the limitations associated with each modality. Differential levels of caution should be applied for each modality, dependent on factors such as thresholding and reliability. This is perhaps most pertinent to the use of tractography in the operating theatre, which should be cautious and qualified, but also applies to fMRI and other functional imaging.

15.3.1.2 Neuronavigation
EpiNav™ was developed in collaboration with Medtronic, and for this reason the export module on the software was designed to communicate with the Medtronic S7 Stealthstation. The generation of 3DMMI in EpiNav™ is therefore tied to implementation of SEEG within a Medtronic framework. Other centres have their own methods for implementing SEEG, which use other neuronavigation software that are described elsewhere. Currently EpiNav™ would not be able to support precise surgical planning in these centres.
15.3.1.3 Clinical workflow

A further limitation is whether the clinical pipeline of 3DMMI can be reproduced in other centres without dedicated support for this. It seems that in other centres that use 3DMMI, there is often one person who drives the use of these tools, at considerable expense of time and cost. In our centre there are two full-time researchers who are responsible for data acquisition, image integration, visualisation and presentation to the clinical teams. It is debatable whether this workload could be incorporated by a busy clinical team, without a ‘driver’ of this technology or formal inclusion into a job plan. One of the aims of the Epinav™ software is that it should be user friendly and readily taken up by other centres. There has been some success with this but the software remains in development, with much work still to be done. This includes the incorporation of pre-processing steps to create a more comprehensive package of functionality that minimises the need for additional software. This also includes the development of a more intuitive and user friendly interface that will be required for more widespread uptake.

15.3.2 Current state

EpiNav™ has been distributed to the following centres for incorporation into their clinical pipelines, with non-disclosure agreements completed.

- Great Ormond Street NHS Trust
- University Medical Centre, Utrecht
- Medical University Vienna
- Cardiff University Brain Imaging Centre

Additionally there has been uptake of EpiNav™ amongst clinical researchers within the UCL Institute of Neurology, for use in imaging research studies.

Ongoing support and training is necessary to deliver the best experience to these centres. Each centre receives a user manual and a clear demonstration of the software by an experienced user using centre-specific data sets. An online support page is currently under
construction that will be available to all end users, and that will provide a forum to describe and address any problems encountered. We envisage this will grow over time, providing a comprehensive source of information for new users. It is also essential that dissemination is limited to controlled software releases that have been thoroughly tested within UCL.

As previously stated it is not possible to offer this software as open source at the present time due to the model of funding, which requires collaboration with a partner in industry. It is hoped that advances in EpiNav™ will be incorporated into next generation neuronavigation and surgical planning platforms, for more widespread uptake.

15.4 Future Studies

15.4.1 Continued development of EpiNav™

The work completed in this thesis describes the foundations for an integrated imaging-guided solution to provide optimised, simplified pipelines in the management of epilepsy surgery. Future work will build on this foundation, to provide a streamlined solution that incorporates all stages of the patient journey.

This includes but is not limited to:

EpiNav™ Strategy: Implementation of library of commonly used intracranial electrode targets and cerebral entry points

- Library of 160 targets and cerebral entry point defined to subgyral level.
- Algorithms and associated software created to enable picklist of target and entry point electrode placement strategy, and warping onto coordinates in individual patients, in addition to bespoke electrode placements that are needed on an individual basis.

EpiNav™ Planner: Computer-assisted electrode trajectory planning
• Computer-assisted electrode trajectory planning software beta tested and used in 20 patients having multiple depth EEG electrodes, with demonstrated increased speed and safety of trajectories.

EpiNav™ Placement: Robot-assisted electrode placement

• Testing of robot integration (iSYS robot) with StealthStation S7 software functioning in neuroimaging laboratory, with a phantom.
• Second iSYS robot functioning in operating theatre, using StealthStation S7 software.
• Randomised comparison of iSYS robot used in operating theatre to guide insertion of depth electrodes compared with current methods.

EpiNav™ Resect: Resection planning in 3D

• Prototype software for delineation of 3D resection volumes and craniotomy created.
• Prototype to import and visualise 4D EEG recorded data and video-telemetry created within EpiNav™.
• Prototype version to map ictal and interictal epileptic activity onto corresponding electrode contacts created within EpiNav™. Ability to select a time point of interest on EEG data and navigate to corresponding time point on video-telemetry to confirm epileptic activity.
• Approximation of epileptogenic zone, based on all data, mapped in EpiNav™ and 3D resection volume.

Dissemination of the complete EpiNav™ solution
15.4.2 Tractography

Additional work should also focus on the use of tractography to guide resections in epilepsy surgery. Visualisation of tractography in the operating theatre is well described. Many groups use this as an adjunct to functional mapping in the awake patient, providing the surgeon with a 3D model of high risk areas, where mapping should be concentrated.

There are two difficulties with this approach. Firstly, there are some patients who are not candidates for awake craniotomies, as they are unable to tolerate the procedure and provide reliable feedback. This is especially pertinent in patients with epilepsy, who may have associated cognitive morbidity. Secondly, there are some functional domains that are difficult to test intra-operatively, such as visual field testing and complex cognitive behaviour. In these cases there is potentially great value in visualising tractography to aid resections in the patient under general anaesthetic.

To illustrate the challenges that need to be overcome we can look more closely at optic radiation tractography, on which some pilot work has been done in chapter 14.

Meyer’s loop is a structure at risk with ATLR, and surgery results in a visual field defect (VFD) in between 48 (Nilsson et al., 2004) and 100% of patients (Barton et al., 2005). Large VFDs prevent patients who are seizure free from driving. This occurs in 13 (Winston et al., 2014)-50% cases (Pathak-Ray et al., 2002), and can have implications on the psychosocial outcomes following surgery (Hamiwka et al., 2011).
There is significant intersubject variability of the anterior extent of Meyer’s loop defined by tractography (Nilsson et al., 2007, Dreessen de Gervai et al., 2014, Lilja et al., 2014, Mandelstam, 2012, Winston et al., 2012b, Yogarajah et al., 2009), and there is a clear post-operative correlation between resections extending into Meyer’s loop and the extent of VFD (Yogarajah et al., 2009, Winston et al., 2012b). Thus a tailored approach to individual patients is helpful to reduce the risk of damaging Meyer’s loop and incurring a VFD following surgery, so long as this does not reduce the chances of seizure freedom following surgery.

There is much interest in the application of optic radiation tractography to avoid surgical damage to Meyer’s loop in ATLR (Winston et al., 2014, Borius et al., 2014, Piper et al., 2014). However, there are very few prospective studies where pre-operative tractography has been superimposed on anatomical imaging in neuronavigation systems to guide the resection (Piper et al., 2014).

Our group has previously developed computational techniques that allow preoperative tractography to be superimposed on intraoperative imaging acquired in the interventional MRI suite operating theatre, allowing compensation for brain shift (Daga et al., 2012). In a prospective cohort of 21 patients, display of the optic radiation within the iMRI operating theatre reduced the severity of VFD and did not affect seizure outcome or extent of hippocampal resection (Winston et al., 2014). This pipeline included corrections for non-linear gradient and susceptibility artefact for all patients, and a non-rigid registration to intraoperative images using custom designed software. Interestingly, there was no significant difference in VFD with the correction for brain shift.

As iMRI is expensive, prolongs surgery and is not widely available this pipeline is unlikely to gain widespread use. In the future, we should aim to reproduce the benefits of the display of the optic radiation in the conventional operating theatre, with a simplified pipeline that may be readily implemented in any Neurosurgical centre using the Medtronic Stealth neuronavigation.
There are several challenges that need to be overcome before a simplified ‘Stealth’ pipeline can be implemented, that can be introduced into the Epinav™ Resect package. These can be divided into two broad categories:

1. Processing tractography

We have now gained experience using the MRtrix software package 0.2.12 (http://www.brain.org.au/software/). Work in chapter 14 has established seed regions and thresholding methods to generate optic radiation tractography, with reasonable inter-rater and intra-rater variability. Further validation of this tractography method should be done prior to implementation in clinical practice.

2. Transferring tractography into the operating theatre

It is essential to ensure that the transfer of generated tracts from the work station to the operating theatre is done in an accurate manner. Although a simplified pipeline is desirable, there are many pitfalls to avoid, and we would recommend that an MRI physicist should be involved in the establishment of this pipeline. Below is a description of these pitfalls that need to be recognised and dealt with appropriately.

15.4.2.1 Distortion corrections

There are two possible sources of distortion.

Gradient non-linearity distortions: Gradient field non-linearity represents a technical imperfection in the gradient that leads to both geometric and intensity distortions. The distortion is specific to the scanner and independent of the patient’s position within the scanner. It is particularly important when different scanners are used, for example when combining preoperative imaging from one scanner with intraoperative imaging from another scanner, and for this reason it is best to limit the number of scanners used. Manufacturer-supplied software corrects only in-plane (in two-dimensions) so distortions remain through plane.
Magnetic susceptibility distortions: A patient in a scanner induces microscopic variations in the magnetic field strength which can result in significant geometric (and intensity) distortions. EPI used for DTI sequences are particularly susceptible to magnetic susceptibility artefacts. As the phase encoding direction is typically anterior-posterior, this is critical when considering the anterior extent of a structure such as the optic radiation. Correction of susceptibility induced distortion may be performed in two ways; either by field map estimation or nonlinear image registration.

15.4.2.2 Registration
A pipeline for registering the results of tractography to neuronavigation T1 should be established. For work in this thesis a rigid registration was employed (ie translation with no deformation), using either AMIRA or EpiNav™ software. For using tractography to guide resections, a more accurate non-rigid registration should be used to ensure correct alignment of the antero-posterior aspect of the optic radiation.

15.4.2.3 Brain shift
Previous work has undertaken a quantitative assessment of the degree of brain shift during ATLR (Winston et al., 2014). There is considerable heterogeneity in the shift seen in the optic radiation and the temporal lobe structures. Within the optic radiation, the maximum displacements were recorded in the anterolateral portion of Meyer’s loop as 6.7-12.8mm (mean 9.3mm). However, the antero-posterior displacement of the anterior tip of the lateral ventricle, which is an important landmark during the surgery, was negligible (1.3mm anterior to 1.3mm posterior, mean magnitude of displacement 0.5mm). These shifts would be difficult to model accurately in the absence of intraoperative imaging. Therefore any attempts to avoid the optic radiation without the benefit of iMRI should factor in a reasonable safety margin by dilating the tracts in isotropic fashion.
15.4.3 Quality Assurance in implementing stereoEEG

Chapter 13 describes a novel method for implementing frameless SEEG in clinical practice. We have shown that this technique has the potential to deliver depth electrodes with acceptable mean target point accuracy given adequate safety margins, and is straightforward to implement. However, we recognise that this technique is not suitable for trajectories that are considered 'high-risk', and does not allow for optimal explorations in all cases. Further, one of the aims of Epinav™ planner is to improve the efficiency of implantations by maximising the placement of depth electrode contacts in grey matter. This requires a submillimetric degree of accuracy of implementation, which is not provided by the current method.

The Epinav™ placement package aims to fulfil this need, delivering submillimetric accuracy with seemless integration into the current surgical workflow. As the Epinav™ pathway develops, with the incorporation of Epinav™ planner and Epinav™ placement, there is a simultaneous need for greater analysis on the accuracy of depth electrode delivery. Previous methods looked at the accuracy of targeting using a measure of the perpendicular lateral shift. A more accurate method should measure accuracy as a Euclidean distance at both the target and entry points. Further the implementation technique should be broken down into its constituent parts, and the accuracy of each step should be prospectively recorded.

The following is a framework for a more comprehensive record of the accuracy of depth electrode delivery. Any future work should include this framework, to examine the gains of any new step introduced into the technique, such as the use of bone fiducials and the incorporation of robotic placement.
Figure 15-2 Schematic representation of framework for assessing accuracy of depth electrode delivery

IEP- intended entry point, ITP- intended target point, AEP- actual entry point, PTP- projected target point, ATP- actual target point

A- Euclidean distance between AEP and IEP (accuracy of finding entry points)
B- Euclidean distance between PTP and IEP (accuracy of finding target points if no electrode deviation)
C- Euclidean distance between ATP and ITP (accuracy of finding target points)
a- angle between ideal trajectory to reach ITP from AEP and projected trajectory (accuracy of manually finding trajectory, drilling and securing bolt)

15.5 Additional research questions

Research questions and requirements that have been raised through the course of this project are listed below:

- Is the added value of 3DMMI reproduced in other centres?
- What is the consensus in the field to added automaton in epilepsy surgery?
- Can CAP be refined with the addition of entry constraints, and incorporated into clinical practice?
- Can CAP be improved to deliver electrode arrangements with fewer trajectories?
- How can the accuracy of frameless SEEG be further improved to approach equivalence with fram-based techniques?
- What are the optimal thresholds and regions of interest for MRtrix tractography of the optic radiation?
- Can a reduction in VFD be demonstrated in the conventional operating theatre with validated optic radiation tractography and distortion corrections?
- Can other association tracts be incorporated into the planning of resective surgery, such as the uncinate fasciculus and superior longitudinal fasciculus?
- Is the relationship between language lateralisation and Meyer’s loop asymmetry seen in the control population?
- Is verbal fluency the best paradigm of fMRI to use when looking for an association with Meyers loop asymmetry?
- Is asymmetry in other white matter tracts such as the uncinate fasciculus related to language lateralisation?
- Can vessel segmentation be improved with non-invasive techniques?

15.6 Clinical Relevance and Final Conclusion

I have supported the continued use of 3DMMI in the epilepsy surgery pipeline at the NHNN using new software dedicated to the task (EpiNav™).

I have demonstrated the clinical usefulness of incorporating 3DMMI in the clinical workflow of planning intracranial depth electrode implantation, and I have completed a pilot study on the advantages of an automated multi-trajectory planner.

I have audited the accuracy of frameless SEEG in a prospective cohort of patients, and I have provided clinical support in the implementation.
I have demonstrated a correlation between Meyer’s loop asymmetry based on tractography, and language lateralisation based on functional MRI, in a historical cohort of patients with epilepsy. However, all patients require an individually tailored approach to resection.

This work lays the foundations for the establishment of an image-guided pipeline for epilepsy surgery delivery, for use at all stages of patient care and by all people involved.


CARDINALE, F. 2015. Stereotactic robotic application accuracy is very high in 'in vivo' procedures. *Stereotact Funct Neurosurg*, 93, 68.


